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American Heart Journal

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Proceedings of the Twentieth Annual Scientific Meeting of the American Heart Association June 6 and 7, 1947

This issue of the AMERICAN HEART JOURNAL includes only scientific papers presented at the Twentieth Annual Meeting of the American Heart Association which was held in Atlantic City, N. J., June 6 and 7, 1947.

THE IMMEDIATE ELECTROCARDIOGRAPHIC EFFECTS OF CIRCUMSCRIBED MYOCARDIAL INJURIES: AN EXPERIMENTAL STUDY

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THE electric phenomena associated with the heartbeat have been analyzed with skill and thoroughness by a number of investigators versed in the physical laws which govern them.[3-9,13,18,20,21] These investigators have done their work so well that the primary task of those whose interest is engaged by these phenomena is no longer the creation of new hypotheses but rather the construction of a rational and consistent system of electrocardiography on the basis of the principles already established. This will require the testing and retesting by experiment and observation of every prediction that these principles suggest, to the end that the limits within which they apply may be defined.

Unless novelty of method affords a fresh approach, any study of the electrocardiographic consequences of myocardial injury is almost certain to be both derivative and repetitive. The methods of the present investigation represent no

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Work done in the Department of Internal Medicine, the University of Michigan Medical School, Ann Arbor, Mich., and the Mayo Clinic, Rochester, Minn. The observations reported in this article were made with the aid of a grant from the Kresge Foundation Fund for Research in Cardiology.

Presented at the Twentieth Annual Meeting of the American Heart Association, held in Atlantic City, June 6-7, 1947.

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radical departure from those applied by others. If justification for this report is to be found, it must be sought in more commonplace qualities. It may be that some of the results recounted here define more boldly the structure of the theory to which they afford little needed confirmation; others may establish the conditions which must obtain in order that the results predicated by that theory may evolve; and finally, a report of the initial confusion provoked by certain findings and resolved by more extended investigation may help others to avoid like dilemmas. We are deeply indebted to Dr. Frank N. Wilson and Dr. Franklin D. Johnston for counsel and suggestions in the course of our experiments.

Development of the membrane theory, elaboration of the laws governing the flow of electric currents in volume conductors, and integration of these concepts with the body of electrocardiographic knowledge lie beyond the scope of this report. An extended survey of these and related problems may be found in an earlier paper which, in conception and expression, bears the mark of finality.[20] It is pertinent only to review aspects of earlier studies which are related directly to the problem of myocardial currents of injury.

Essential to the production of a current of injury is the existence in the myocardium of a region on one side of which the cell membranes are damaged more severely than on the other. The side of this zone where the injury is most severe may be bounded by a layer of muscle which has been destroyed completely. If dead, this muscle layer has no part in the reactions under consideration and acts only as a portion of the volume conductor surrounding the injured tissue. On the other side of this zone of injury are fibers which may be termed normal in respect to three arbitrarily defined criteria:

1. When the fibers are in the resting phase, a potential difference is maintained across the cell membrane. This potential difference is the product of an orderly orientation of ions disposed in such a way that the external surface of the membrane is positive relative to the internal surface.

2. On the arrival of the excitatory process, a redistribution of ions occurs at the cell membrane attended by a profound alteration of the potential difference between the internal and external aspects of that membrane. This reaction is called depolarization.

3. Following the response to the excitatory impulse with depolarization of the cell membrane, a reorientation of ions occurs with the restitution of the original potential difference across the membrane. This reaction is called repolarization.

Characteristic, then, of fibers lying just outside the zone of injury is the maintenance of a fully polarized membrane during diastole, the occurrence of depolarization on arrival of the excitatory impulse and the restitution of a state of full polarization of the cell membrane following response to the excitatory process.

In what respect does muscle within the zone of injury differ from that which responds to excitation in a manner considered characteristic of the normal myocardium? Two variations may be defined:

1. The voltage across the membrane of the injured fibers may be zero or may reach any fraction of its normal value. The degree of polarization may

vary not only in different portions of the region of injury but also over different portions of the membrane of one and the same fiber. The potential difference across the membrane will, in general, be greatest in the fibers or parts of fibers which have been injured least.

2. On arrival of the excitatory impulse the injured tissue may respond, undergoing the changes of ionic distribution characteristic of this reaction. The possibility exists, however, that some of the fibers in the area of injury do not respond or that only a part of the cell membrane becomes depolarized, the remainder retaining across its surface the potential difference which existed during the resting state.

Muscle within the zone of injury exhibits, therefore, in comparison with that within the "normal" region a reduction, variable in degree, of the voltage across the cell membranes during the resting phase. In addition, some of the injured fibers or portions of fibers may display a state of refractoriness to the excitatory impulse. In a diagrammatic way, the difference between the fibers in the "normal" region and those in the injured region relative to the state of polarization of the cell membrane may be represented as in Fig. 1. In the un-

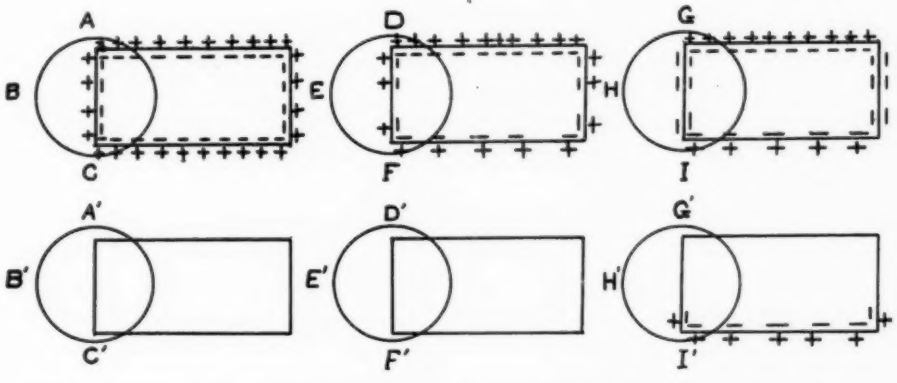

Fig. 1.—Diagrammatic representation of normal and injured cells with respect to the state of polarization existing at the cell membranes during the resting and active stages. For explanation, see text.

injured resting fibers, the voltage across the cell membrane is maximal for cells of this type. The potential difference between the inside and outside of that membrane is the same for all its parts. Hence any possible circuit, ABC, passing through the cell necessarily includes potential drops of which the algebraic sum is zero. This condition which exists in the resting normal fiber obtains also when that fiber has responded to the excitatory process and its membrane is depolarized. Any potential differences maintained at the cell membrane are the same for all its parts and no electromotive force is contributed to any circuit, $A'B'C'$, passing through it.

Only under two circumstances does the normal cell generate an imbalanced electromotive force. It does this as it passes from the resting into the active state, during which time depolarization occurs, and when it passes back from

the active into the resting state during the repolarization process. The normal cell does not contribute to the production of the current of injury.

The source of the current of injury lies within the traumatized tissue. Its existence depends on the first of those two characteristics peculiar to injured fibers. It flows because of variations of voltage across different portions of the cell membranes in the damaged muscle. When traumatized myocardium is included between the terminals of the galvanometer, that part of the current of injury flowing through the instrument is neutralized by a compensating current. Hence, if the current of injury flowed uninterruptedly, its existence would have no effect on the electrocardiogram. The immediate source of the changes in the part of the electrocardiogram inscribed after myocardial excitation is completed must be sought in that second characteristic of traumatized fibers, the peculiarities in their response to the excitatory impulse. If a response occurs in these cells and their membranes are depolarized in greater or lesser degree, then all or part of the current of injury will disappear (Fig. 1, circuits *DEF* and *D'E'F'*). A corresponding fraction of the neutralizing current introduced in the galvanometer will flow unopposed until repolarization occurs. If, on the other hand, certain fibers or parts of fibers in the traumatized muscle are refractory to the excitatory impulse, the situation represented in Fig. 1, circuits *GHI* and *G'H'I'*, may develop. Because the more strongly polarized portion of the cell membrane responds while the remainder does not, an electromotive force will be generated directed in a sense opposite to that of the voltage responsible for the current of injury.

The displacement of the RS-T segment commonly occurring in the presence of acute myocardial injury is a manifestation of the flow of current produced by the electromotive force derived from the refractory portion of the cell membrane combined with some portion of the neutralizing current. The exact importance from the quantitative standpoint of each of these sources of current remains unknown. That monophasic curves can be recorded in the absence of significant myocardial injury has been demonstrated by Ashman and Woody.[1] Deflections of this kind developed when the spread of excitation was blocked at a junction between uncooled and cooled tissue, probably as a result of prolongation of the refractory period in the cooled fibers of the heart muscle. Furthermore, Eyster and associates[10] observed that the displacement of the RS-T segment which occurred at the inception of a myocardial injury exceeded the coincident shift in the diastolic base line of the electrocardiogram. This latter alteration is produced by the current of injury prior to its neutralization by the compensating current and is a measure of its intensity.

These observations afford support to the conclusion that the displacement of the RS-T segment following acute myocardial trauma is not dependent solely on a reduction of the intensity of the current of injury when excitation is complete. It is possible that this displacement is unrelated to alterations of the flow of the current of injury, and is a manifestation only of the imbalance of electromotive forces at the cell membranes within the injured region consequent to variations of their response to the excitatory impulse.

Both the direction and the amount of RS-T displacement produced by an acute myocardial injury depend on the spatial orientation of the injured tissue relative to the electrodes of the galvanometer. If the potential at the indifferent electrode is not influenced significantly by voltages generated within the heart, then the electrocardiogram will afford an uncomplicated record of the changes of potential at the exploring electrode. If the solid angle subtended at the exploring electrode by the bounding surfaces of the damaged muscle includes only portions of those surfaces on which lie the more severely injured cells, the potential at the electrode will be positive during inscription of the RS-T segment. The potential at this period will be negative if the angle subtended at the exploring electrode includes only the less severely injured cells (Fig. 2). If the configuration and orientation of the zone of injury is such that the angle subtended at the exploring electrode by the bounding surfaces of the lesion includes cells of both types, then the potential at the electrode will be the algebraic sum of the electric forces which would be produced by each group of cells in the absence of the other.

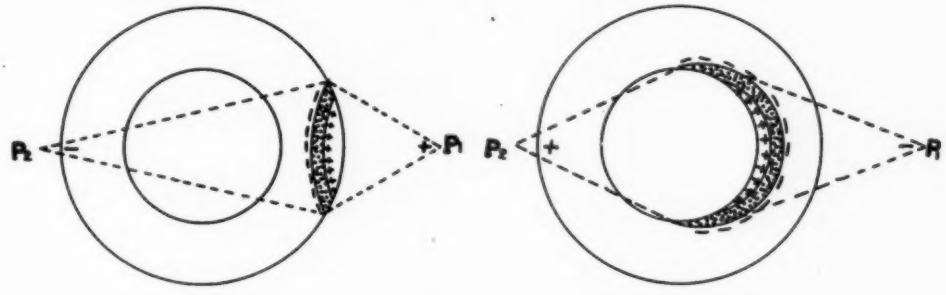

Fig. 2.—*A*, Diagrammatic representation of the electric field produced at the end of the QRS interval by a region of injured muscle on the epicardial aspect of the ventricular wall. The field is similar to the one which would be produced if the injured muscle (dotted zone) were polarized in the sense indicated. (After Wilson, Hill, and Johnston,[18] 1934.) *B* represents the field produced by a layer of injured muscle confined to the subendocardial region.

In so brief and dogmatic a statement of the conceptions of the dipole theory as they are related to myocardial injury, accuracy has been sacrificed and ignorance has been veiled. An attempt has been made to arrive at certain points of departure, points which are fundamental in the realm of theory and points which may be tested experimentally.

EPICARDIAL LESIONS

The electrocardiographic phenomena produced by injuring the heart have been investigated carefully.[6,18 20-22] Wilson and associates[19] in 1934 burned the subepicardial muscle of the ventricle of turtle hearts. Electrocardiograms were recorded with the indifferent electrode placed at a point remote from the heart and with the exploring electrode near or in contact with the ventricular surface. They observed that, apart from a difference of magnitude, the variations of po-

tential at a given point on the ventral surface of the beating heart were similar in all respects whether this surface was exposed to air or was in contact with an external conducting medium. When the muscle beneath the exploring electrode was injured, pronounced displacement of the RS-T segment occurred and the ventricular complex often became monophasic. With connections made so that relative negativity of the exploring electrode produced an upward deflection, the direction of the RS-T displacement was downward. When the subepicardial muscle was injured over a wide area and the injury and the exploring electrode were on opposite sides of the heart, the RS-T displacement was upward and was less pronounced. These investigators analyzed the electric field produced by the injury. It is their conception of this field which forms the basis for Fig. 2, *A*.

During the course of studies designed to ascertain the effects of lesions involving only the subendocardial layers of muscle, occasion arose to repeat certain procedures of these earlier investigations. In several experiments, observations were made on lesions involving the subepicardial muscle of that portion of the ventral surface which was exposed to air. Electrocardiograms in which relative negativity at the exploring electrode was represented by a downward deflection showed pronounced upward displacement of the RS-T segment when the exploring electrode was on the epicardial aspect of the lesion. However, curves derived from an exploring electrode in the ventricular cavity did not show the distinct downward displacement of the RS-T segment that had been anticipated.

In the experiments of Wilson and associates, the potential inside of the ventricular cavity was not recorded. However, when the subepicardial muscle of the dorsal myocardial wall was burned, relative negativity of the epicardium on the ventral wall was recorded during the RS-T period. If the conductivity of the body tissues is relatively uniform, the electric field corresponding to the forces arising within the injured muscle should be approximately symmetric with respect to the bounding surfaces of that damaged tissue. This being the case, one would expect that in the presence of an acute lesion of the dorsal epicardium, negativity of the ventral epicardium would be attended by negativity of the ventricular cavity (Fig. 2, *A*).

An obvious discrepancy existed between the preliminary observations of the present investigation and the results predicated on the basis of the conceptions of Wilson and associates. The experiment of the earlier investigation, therefore, was repeated with the intent of recording simultaneously the potential changes in the ventricular cavity and those at the epicardial surface.

Method.—Experiments were performed on turtles (*Graptemys geographica*). The animal was pithed, the heart was exposed by removing the plastron and the preparation was placed with the dorsal side down in a large shallow dish filled with Ringer's solution. A Sanborn Tribeam electrocardiograph was used to obtain two simultaneous records on the same strip of paper. One terminal of each circuit of the instrument was attached to a copper disk 5 cm. in diameter. This electrode was placed in the Ringer's solution at a point as remote as possible from the heart. The other terminal of each circuit was attached to one of the

exploring electrodes. When points on the surface of the heart were to be explored, the electrode consisted of a small glass tube stoppered with salted kaolin and filled with 20 per cent copper sulfate solution into which was thrust a coil of copper wire. Contact with the heart was made by a wick of cotton embedded in the kaolin plug and enclosed in a small rubber tube so that it was insulated to within 1 or 2 mm. of its exposed end. When the potentials within the ventricular cavity were to be recorded, the electrode consisted of a filiform catheter with a core of copper wire. The insulation of the catheter covered all but the tip of the copper wire. The lesions produced in the subepicardial muscle were burns made with a high frequency electrocoagulation unit (Bovie).

Experiment 1.—The turtle was prepared in the usual manner. The filiform electrode was introduced into the ventricular cavity. This was accomplished by making a small incision in the lateral subdivision of the right aorta. The tip of the electrode was slipped into the ventricular cavity and a ligature encircling the artery in which lay the shaft of the electrode was drawn tight. The soft-tipped electrode was placed on the part of the ventral surface exposed to air and simultaneous records were made of the ventricular cavity and epicardial potentials. The epicardial electrode was then removed temporarily. With the electrocoagulation unit, a burn was made on the dorsum of the ventricle. This lesion covered the left half of the basal portion of the dorsal epicardial surface. The soft-tipped electrode was replaced on the epicardium and another set of electrocardiograms was recorded immediately. Subsequent electrocardiograms were made five minutes, twenty-five minutes, and forty minutes after production of the lesion.

The electrocardiograms recorded in Experiment 1 are reproduced in Fig. 3. Downward displacement of the RS-T segment is present in the curves obtained after production of the lesion with the exploring electrode in the ventricular cavity and also in those taken with this electrode on the portion of the ventricular surface which was exposed to air. The amount of displacement is greatest in records obtained immediately after the lesion was produced. Within twenty-five minutes the RS-T segment had returned almost to the isoelectric line in both the epicardial and the cavity leads.

These results are in complete accord with those reported by Wilson and associates and with the conception of the electric field which they advanced. But this confirmation of their observations defined with even greater precision the problem which remained unsolved. Why should the potential within the ventricular cavity be made negative during the inscription of the RS-T segment by an acute lesion affecting the dorsal subepicardial muscle, but remain unchanged when a similar lesion of the ventral subepicardial muscle was produced? The major difference between the two lesions did not appear to be an intrinsic one. In each instance the orientation of the injured and the uninjured muscle relative to the exploring electrode in the ventricular cavity was the same. But a major difference did exist in the environment of the lesion. The injured area on the dorsal surface was completely surrounded by a conducting medium

whereas that on the ventral surface was bounded on one side by air. Determination of the effect of eliminating this difference afforded an attractive approach to the problem under investigation.

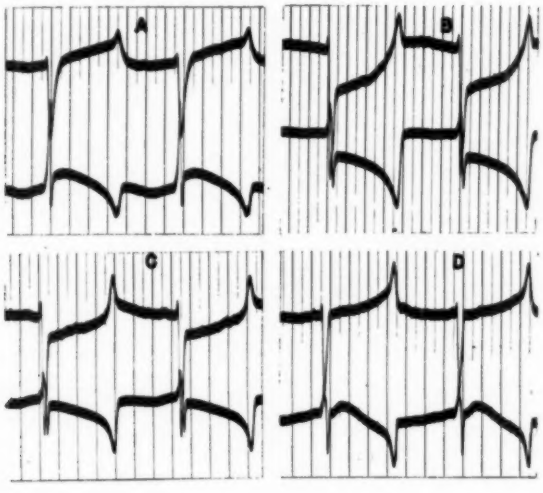

Fig. 3.—Upper curves were recorded with the exploring electrode in the ventricular cavity; lower curves, with the electrode on the portion of the ventricular wall exposed to air. Exact sensitivity is uncertain but it approximates 3 millivolts per centimeter on the ordinate scale. *A*, Control; *B*, after burning dorsal surface of the ventricle; *C*, five minutes after burn; and *D*, forty minutes after burn.

Experiment 2.—The turtle was prepared in exactly the same manner as in Experiment 1. Electrocardiograms were taken with the exploring electrode of one circuit in the ventricular cavity and that of the other on the portion of the ventral surface exposed to air. A circular pad of cotton, approximately 3 mm. thick and large enough to cover the ventral surface of the heart and extend into the surrounding medium, was soaked in Ringer's solution and laid over the heart. The soft-tipped electrode was placed in contact with the surface of this pad at a site as near as possible to its previous point of contact with the ventricular surface. Another set of electrocardiograms was made. When the pad lay on the heart, the size of the deflections of the ventricular complex was reduced to approximately a fifth the amplitude of the deflections obtained when the exploring electrode rested on the exposed surface of the heart. In order to maintain approximate constancy of the size of the deflections recorded under the two sets of conditions, the sensitivity of the circuit was increased fivefold when curves were taken with the pad covering the heart.

The pad was then removed and with the electrocoagulation unit a burn was made on the exposed portion of the ventral surface of the heart. Thereafter, electrocardiograms were recorded in the same manner and in the same order as the curves taken before the burn. Additional sets of electrocardiograms were made ten minutes, twenty minutes, and fifty minutes later.

The electrocardiograms recorded in Experiment 2 are reproduced in Fig. 4. Examination of these curves reveals that upward displacement of the RS-T

segment is present in those derived from the epicardial electrode after production of the lesion whether the ventral surface was or was not immersed in the conducting medium. On the other hand, downward displacement of the RS-T segment is present in the leads from the electrode in the ventricular cavity only when these were taken while the ventral surface of the heart was covered by the pad soaked in Ringer's solution.

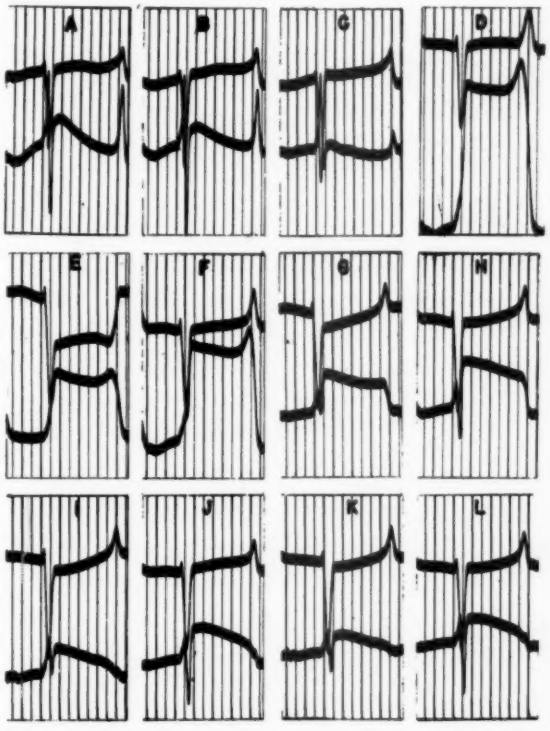

Fig. 4.—Upper curves were recorded with the exploring electrode in the ventricular cavity; lower curves, with the electrode on or adjacent to the epicardial aspect of the ventral wall of the heart. *A*, Control prior to immersing the dorsal surface of the heart in Ringer's solution; *B*, control after immersion of the dorsal surface; *C*, control with ventral surface of the heart covered by a pad soaked in Ringer's solution; *D*, after burning ventral surface of heart, lesion and ventral wall of heart exposed to air; *E*, immediately after *D*, ventral surface of heart covered with a pad soaked in Ringer's solution; *F*, immediately after *E*, pad removed from ventral surface of heart; *G*, ten minutes after burn, pad over heart; *H*, immediately after *G*, pad removed from surface of heart; *I*, twenty mintues after burn, pad over heart; *J*, immediately after *I*, pad removed from surface of heart; *K*, fifty minutes after burn, pad over heart; and *L*, immediately after *K*, pad removed from surface of heart.

Ordinate scale: upper curves, 5 millivolts per centimeter; lower curves, 3.5 millivolts per centimeter except when ventral surface of heart was covered by pad, then 0.5 millivolt per centimeter.

It has been observed by others that the distribution of electric forces arising within a region of injury is dependent on environmental factors. Craib[4] found that the potential at the surface of a partially immersed strip of injured skeletal muscle varied with the position of the injured tissue relative to the conducting medium. Eyster and associates[10] in 1938 commented on the minor changes in the potential of the medium surrounding an isolated quiescent tortoise heart

following injury if the heart were not immersed or if the plane of injury corresponded to that of the field.

It is questionable how much will be gained from an effort to conceive the exact origin and distribution of potential variations within an electric field under the circumstances described in Experiment 2. An analysis will be presented only after according recognition to the fact that it is an explanation designed to fit a limited set of circumstances.

Suppose that a sheet of heart muscle could be isolated in an untraumatized state and then injured in such a way that the cells on one side of the sheet were damaged more severely than those on the other side. A gradient of injury would then exist across the muscle, and current* would flow from the least injured cells on one side to the most injured cells on the other. Within this isolated strip of muscle there must be complete circuits containing the algebraic sum of all the potential drops between the least injured side of the least injured fibers and the most injured side of the most injured fibers. If one electrode were placed on one surface of the sheet and the second electrode on the other surface, the potential difference between the two sides could be measured. Immersion of the muscle in a conducting medium would not be essential to any of these developments.

Suppose the surface of this muscle on which lay only the least injured aspects of the least injured cells was placed in contact with a conducting medium of large extent. All points on this surface would be at the same potential and hence no current would flow between them.

Finally, suppose that both surfaces of the injured muscle were immersed in the conducting medium. Innumerable circuits would now exist, running from the least injured fibers through the conducting medium and back into the muscle sheet on the side where lay the most injured cells.

Thus, if an acutely injured muscle in which a gradient of injury exists is to create an electric field in a conducting medium of large extent, cells lying at different levels on the gradient of injury must make contact with the medium.

Under the circumstances existing when the electrocardiograms reproduced in Fig. 4, *D* were recorded, only the least injured fibers made contact with the medium. Hence, no significant amount of current flowed from the injured tissue into the conducting medium. When one electrode of the galvanometer was connected to the most severely injured cells and the other terminal to the reference electrode in the medium, a circuit was completed and the potential difference across the traumatized tissue was recorded. However, only after the more severely injured fibers were immersed in the medium did any appreciable fraction of the current of injury flow through the ventricular cavity and thence into the circuit of the galvanometer to which the electrode in the cavity was connected.

This analysis appears to afford a reasonably satisfactory explanation for the developments in Experiment 2. It does not lend itself easily to the explanation of even minor alterations in the conditions which existed in that experi-

*In this description, the term "current of injury" is used in the broadest sense. The exact source of the current responsible for RS-T displacement in the electrocardiogram is immaterial to the argument.

ment. In order to arrive at a method more generally applicable, it is necessary to adopt a procedure commonly utilized in computing electric fields in heterogeneous media.[15] This approach, known as the method of images, may be applied in the analysis of problems in which two media are separated by a plane boundary. In Fig. 5, part 1, let the line AB represent a plane surface

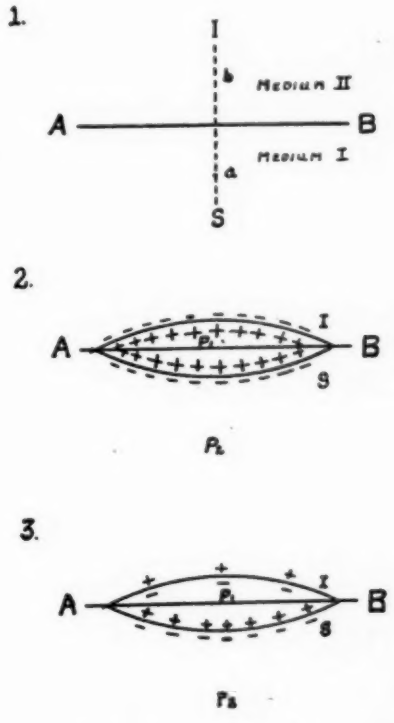

Fig. 5.—The method of images as it applies to the solution of the problem presented by the results of Experiment 2. In all three diagrams, the line AB represents a plane which forms the boundary between two mediums of different conductivities. S represents a source of electricity in Medium I and I represents its image forces in Medium II. For further discussion, see text.

which constitutes the boundary between two media. Let us suppose that there is a source S of electricity in Medium I at a distance a from the plane surface. Let I in the second medium be the image of S, and let k_1 be the resistance of Medium I and k_2 the resistance of Medium II. It can be demonstrated that the flow of current at any point in the first medium is the same as would be produced by the source S, together with a source $\frac{k_2 - k_1}{k_1 + k_2} S$ placed at I, if the first medium were infinite in all directions. The current at a point in the second medium is the same as would be produced by a source $\frac{2k_2 S}{k_1 + k_2}$ placed at S if the second medium were infinite in all directions.

If the second medium is a perfect insulator, then k_2 is equal to infinity and by the first equation the image at I would be equal to the source at S and of the same sign.

In Experiment 2 the source S in the first medium was represented by the injured layer of muscle, one aspect of which was bounded by a volume conductor of large extent and the other by a nearly perfect insulator, air. The effect of this environmental situation on the distribution of electric forces produced by the lesion may be estimated by applying the method of images. Because the medium on one side of the boundary was a nearly perfect insulator, the images at I and the forces at S would be of the same sign and of equal magnitude. In Fig. 5, part 2, the forces produced by the lesion are represented diagrammatically by a polarized surface S, seen in section. The image forces I are indicated in the same way. It will be seen that the polarized surface S and its image I form a closed space. The positive poles of the elementary voltages are inside this space, the negative poles outside.

At any point P_1 on the epicardial surface of the lesion, the solid angle subtended by the polarized surface S and that subtended by its image I have the same sign and equal magnitude. At any point P_2 which lies outside the injured muscle, the two angles are opposite in sign and equal in magnitude. The potential at any point due to an injured region is roughly proportional to the solid angle which the bounding surfaces of the lesion subtend at that point. It is clear, therefore, that the potential at the epicardial surface of the lesion under consideration would be positive and double what it would be if the medium surrounding the injured muscle were infinite in all directions. The potential at any point outside the zone of injury, on the other hand, would not be influenced significantly by electric forces produced within the damaged muscle.

When the surface of the heart was covered by a pad soaked in Ringer's solution, an environmental situation was created in which the injured layer of muscle was bounded on its epicardial aspect by a medium of higher conductivity than that which lay on the opposite side of the zone of injury. Under such circumstances, by equation 1, the images at I and the forces at S would be of opposite sign and of a magnitude determined by the relative conductivity of the mediums and their extent (Fig. 5, part 3). As a result, the degree of positivity at P_1 would be reduced greatly and significant negativity would develop at P_2.

An Experiment With Muscle Juice (Experiment 3).—This experiment does not constitute an integral component of the series. It is described because, to us, the results seemed particularly interesting.

The sequence of changes in myocardial injury probably includes (1) an increase of the permeability of the cell membranes; (2) a redistribution of the ions on either side of the cell membranes, and (3) a diminution of the voltage across these membranes, the degree of which is proportional to the severity of the injury.

There is reason to believe that, in these changes which occur after injury, potassium ions are involved. A consideration of the intimate nature of the part which these ions play would extend beyond the authors' knowledge. Two well-

established facts may be cited: (1) The concentration of potassium ions is much higher in intracellular than in extracellular fluids. (2) If a solution containing potassium ions in relatively low concentration (0.1 molar potassium chloride) is applied to the surface of the heart and the exploring electrode is placed on the same area, ventricular complexes of a monophasic type are recorded.

If injuring the cell increases the permeability of its membrane, it undoubtedly leads to diffusion of potassium ions from the intracellular to the extracellular fluid. These potassium ions may be expected to exert on the less severely injured and uninjured muscle an effect similar to that produced by a solution of 0.1 molar potassium chloride. As a minor and perhaps repetitious study of this phenomenon, the following experiment was undertaken.

A turtle was prepared in the manner already described, and control electrocardiograms were taken in the usual way. A small piece of skeletal muscle from the pelvic girdle of the same turtle was chopped into fine pieces and a few drops of juice were squeezed from the macerated tissue onto a piece of dry cotton 8 mm. in diameter. This piece of cotton was laid on the air-exposed portion of the ventricle of the beating heart. The wick of the soft-tipped electrode was placed in contact with the piece of cotton. Two sets of tracings were made. In a second piece of cotton, 3 cm. in diameter, a hole approximately 8 mm. in diameter was cut. This pad was soaked in Ringer's solution and placed on the surface of the heart in such a way that the borders of the hole made con-

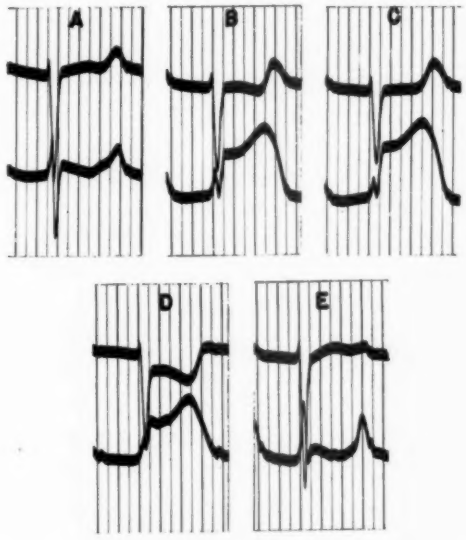

Fig. 6.—Upper curves were recorded with the exploring electrode in the ventricular cavity; lower curves, with the exploring electrode on or adjacent to the ventral aspect of the heart wall. *A*, Control; epicardial electrode resting on surface of heart; *B*, after placing small pad soaked in muscle juice between the epicardial electrode and the ventral surface of the heart; *C*, one minute after *B*, conditions unchanged; *D*, two minutes after *B*, air-exposed portion of ventral surface covered by a cotton pad soaked in Ringer's solution; and *E*, after both pads had been removed and surface had been rinsed repeatedly with Ringer's solution.

Ordinate scale: upper curves, 5 millivolts per centimeter; lower curves, 3.5 millivolts per centimeter except in *D*, where a scale of 0.8 millivolt per centimeter existed.

tact with the margins of the pad soaked in cellular juice. Another set of electrocardiograms was recorded. Both cotton pads were removed and the surface of the heart was rinsed repeatedly with Ringer's solution. A final set of electrocardiograms was recorded.

The electrocardiograms recorded in Experiment 3 are reproduced in Fig. 6. In the curves derived from the electrode placed in contact with the small cotton pledget soaked in muscle juice, upward displacement of the RS-T segment was always present. Downward displacement of the segment occurred in leads from the electrode in the ventricular cavity only when the exposed surface of the heart was covered with a larger pad soaked in Ringer's solution. These findings are similar to those obtained when the subepicardial muscle at a comparable site was burned.

The results of this experiment indicate that in the fluid which can be squeezed from severely damaged muscle cells of a turtle there is a substance which, when applied to the beating heart of the same animal, will produce changes in its action currents like those which follow injury inflicted on the myocardial cells by mechanical or thermal means.

ENDOCARDIAL AND SUBENDOCARDIAL LESIONS

Large myocardial infarcts which involve only the subendocardial muscle occur very rarely in man and lesions of this kind are difficult to produce in animals. Hence, the electrocardiographic changes related to acute injuries in the subendocardial region have remained problematic. It seems to be generally agreed that such lesions produce depression of the RS-T segment in the standard limb leads and often in the precordial leads as well. Wolferth and associates[22] recently have proposed certain generalizations in explanation of this phenomenon. They divided RS-T displacements into primary and secondary types, defined as follows: displacement of the primary type results from physicochemical disturbances in the fibers directly beneath the exploring electrode; displacement of the secondary type is recorded over the surface of uninvolved muscle as a result of changes of potential produced at that surface by forces generated in injured muscle elsewhere in the heart. In the language of Lewis and Rothschild, the first is intrinsic and the second extrinsic in origin. In the experimental results reported by Wolferth and associates,[22] primary RS-T displacement, with one possible exception, was always positive and secondary displacement always negative. Since endocardial lesions consistently bear a secondary or extrinsic relation to an electrode placed on the epicardial surface of the heart, the resulting displacement of the RS-T segment is downward.

Between the predictions based on these generalizations and those derived from the concepts of the dipole theory outlined, there is seldom a significant difference. However, on the basis of the dipole theory, an endocardial lesion may produce upward displacement of the RS-T segment in a lead from an electrode placed on an uninjured epicardial surface. This possibility is illustrated in Fig. 2, *B*, in which a subendocardial lesion is represented. An electrode placed at P_1 lies in a portion of the cardiac field which should be at a negative potential

at the end of the QRS interval. Under the circumstances postulated, an electrode placed at P_2 on the epicardial wall opposite the lesion would lie in the positive portion of the field and in a lead from this point the RS-T segment would be displaced upward.

Consideration of these relationships identifies one requirement which should be satisfied in an investigation of the electrocardiographic changes produced by acute subendocardial injuries. Curves should be recorded not only from points on the epicardium overlying the injured muscle but also from the epicardial surface of uninvolved parts of the ventricular walls.

The difficulties encountered in attempts to produce endocardial lesions justify extended consideration of other aspects of this problem. If the effects of damage to the endocardial and subendocardial tissue on the potential at an electrode outside the heart are to be ascertained, then the lesion must be satisfactory in certain respects.

1. It should be large enough and severe enough to generate an electric field of measureable intensity in the conducting medium surrounding the heart.

2. The boundaries of the lesion should meet the following specifications: first, the zone of damage should be thin, so that a layer of uninjured cells lies between the traumatized tissue and the epicardium; and second, the injured cells should be oriented in such a way that all the electric forces produced by them have a similar effect on the potential of an electrode placed on one side of the lesion.

The production of a lesion which meets these requirements is not accomplished easily nor frequently. The very architecture of the heart renders difficult their fulfillment. The epicardium presents a relatively broad smooth surface readily accessible to traumatizing procedures. The area of the endocardial surface is much smaller, its configuration is irregular and its approach is difficult. If a lesion is to be large and still meet the demand that all its parts contribute forces of like sign to the electric field, then it must involve most of the endocardial aspect of either the ventral or the dorsal wall of the ventricle without extending into the endocardial tissues on the opposite side of the ventricular cavity. Experience soon reveals that in the production of so large a lesion on one wall, injury to the other wall is likely to occur, particularly near the apex.

Limitation of the thickness of the traumatized zone can be achieved more satisfactorily by the electrocoagulation technique than by any other method which we have devised. Yet an unusually prolonged or intense flow of the traumatizing current may result in extension of the injury to the epicardial tissues.

The two experiments described here were selected from a series of thirty-five. In these two instances among all the experiments the electrocardiographic changes were greatest, but in them also the criteria defined in the preceding paragraphs were most nearly fulfilled.

Method.—Turtles were used. The earlier experiments were undertaken on small specimens (*Graptemys geographica*) measuring 6 to 8 inches (15 to 20 cm.) in diameter. In such animals the heart is small and the production of a well-localized subendocardial lesion was found to be exceedingly difficult. Large

snapping turtles (*Chelydra serpentina*) were then secured. Each of these animals measured 12 to 14 inches (30 to 36 cm.) in diameter and weighed approximately 10 pounds (4.5 kilograms). Following an initial series of experiments on twenty small turtles, a second series was carried out on fifteen of the larger animals. An endocardial lesion of some type was produced in all except two of these turtles.

The myocardium was injured by electrocoagulation. The method was identical with that employed in damaging the subepicardial tissues. In the experiments on small turtles, the filiform electrode previously described was introduced into the ventricular cavity by way of the lateral branch of the right aorta. This electrode was used both for recording potentials in the ventricular cavity and for applying the electrocoagulating current. In the experiments on the larger turtles, an enameled copper wire 1.2 mm. thick with a rounded tip was substituted for the filiform electrode.

The large turtles were not placed in a dish filled with Ringer's solution. In the experiments performed on them, the indifferent electrode was a copper disk, 2 cm. in diameter, placed on the subcutaneous tissues of the left hind leg.

Experiment 4.—This was an experiment on a small turtle. The animal was prepared in the usual manner. Two leads were taken simultaneously; one recorded the potential of the ventricular cavity, and the other, the potential at a point on the central portion of the exposed ventricular surface. With the filiform electrode attached to the electrocoagulation unit, an endocardial burn was made. Electrocardiograms were made in rapid succession under conditions noted in the legend of Fig. 7.

Post-mortem examination of the heart revealed a lesion involving the entire endocardial aspect of that portion of the ventral wall lying to the left of the band of muscle which represents the primordial septum. The apparent thickness of this lesion was 1 mm. or less.

Electrocardiograms recorded in Experiment 4 are reproduced in Fig. 7. The results of this experiment are presented for two reasons. The first of these is that the curves obtained exhibit displacement of the RS-T segment induced by extensive injury of subendocardial tissues of the ventral wall of the heart. The contrast between the electric field on one side and that on the opposite side of the injured region is illustrated. The RS-T displacement in the leads from the epicardial electrode is downward, whereas, in those from the cavity electrode, the RS-T displacement is upward. These findings are consistent with the postulates of the dipole theory.

The second reason for presenting these data is that they illustrate a problem which arose frequently in this series of experiments; namely, the effect on the form of the electrocardiogram of changes in the electrical properties of the immediate environment of the heart. In Experiment 2, an example of this effect as it occurs in epicardial lesions was presented and discussed at length. Review of the electrocardiograms reproduced in Fig. 7 indicated to the observers that in the presence of endocardial injury an abundance of free fluid on the surface of the heart has an effect similar to that produced by covering the air-exposed

portion of the surface with a thin cotton pad soaked in Ringer's solution. Either of these environmental factors could be effective in one or both of two ways: either by altering the distribution of cardiac currents or by changing the nature of the contact between the soft-tipped electrode and the ventricular surface. When all free fluid is removed from the air-exposed portion of the ventral surface of the heart and from the cotton wick at the tip of the exploring electrode, the area of contact between the epicardial surface and the wick is small and is subject to variations during different portions of the cardiac cycle. A relatively constant contact can be effected only by pressing the wick of the electrode firmly

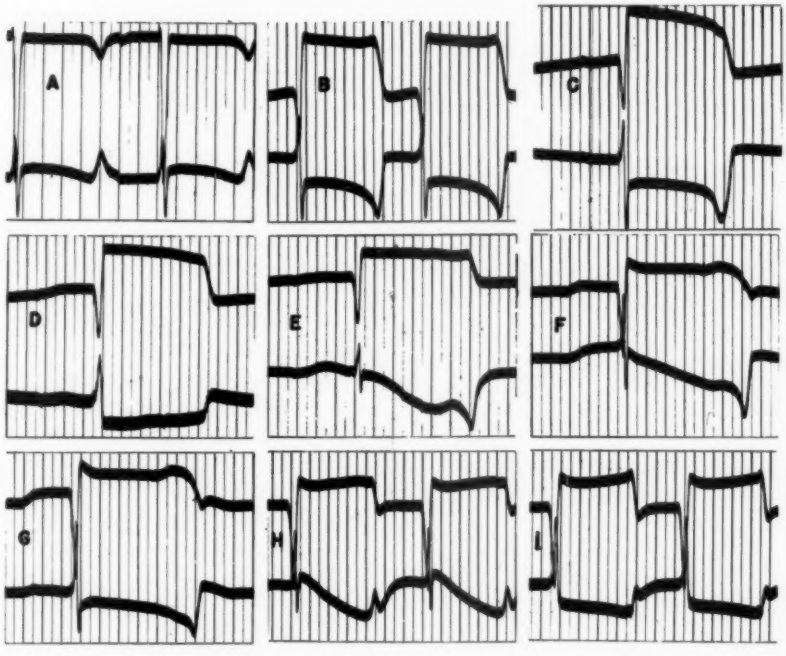

Fig. 7.—Upper curves were recorded with the exploring electrode in the ventricular cavity; lower curves with the exploring electrode on or adjacent to the epicardial aspect of the ventral wall of the heart. *A*, Control; *B*, after making a burn on the endocardial aspect of the ventral wall of the heart, ventral surface of heart partially immersed in Ringer's solution; *C*, immediately after *B*, 2:1 auriculoventricular block had developed and persisted until curves reproduced in *H* were recorded; *D*, air-exposed portion of ventral surface of heart covered by a pad soaked in Ringer's solution; *E*, after removing all fluid from ventral surface of heart; *F*, five minutes after burn, no free fluid on ventral surface of heart; *G*, immediately after *F*, pad covering heart; *H*, ten minutes after burn, all free fluid removed; and *I*, immediately after *H*, pad covering ventral surface of heart.

Sensitivity of galvanometer circuit was increased approximately fivefold in recording curves from epicardial electrode when pad soaked in Ringer's solution covered ventral surface of heart.

against the epicardium. However, this procedure may itself injure the subepicardial muscle and produce changes in the form of the electrocardiogram. Covering the heart with a pad soaked in Ringer's solution or immersing it in free fluid permits the establishment of a constant contact between the heart and the exploring electrode.

It is difficult to ascertain whether the changes in the electrocardiogram which attended immersion of the heart in Experiment 4 were related primarily to alterations of the electric field produced by the injured muscle or to the establishment of a better contact between the electrode wick and the cardiac surface. These changes were not striking in leads from the electrode within the ventricular cavity. In such curves the upward RS-T displacement was slightly greater when a pad covered the heart than it was when the ventricular surface was exposed to air (Fig. 7, *H* and *I*). With the same variation in the environmental circumstances a greater change occurred in leads from an electrode placed at a point outside the heart. When the ventral surface of the heart was bounded by air, the junction of the S wave and the S-T segment was above the isoelectric line in an epicardial lead from the exposed region. In a similar lead taken with a pad covering the heart, this junction was on a level below the isoelectric line near the point occupied by the spike of the S wave in the preceding curves.

It appears probable that most of these changes in the ventricular complexes of leads from the epicardium were due to variation in the contact made by the electrode with the heart. The conclusion is not justified, however, that all of them certainly were related to this factor. If an alteration of the electric field produced by the lesion did occur, the origin of the change may have been similar to that postulated in the discussion of a similar situation which obtained in Experiment 2.

Experiment 5.—This experiment was performed on a large turtle. The animal was prepared in the usual manner. In order to obtain electrocardiograms from the dorsal epicardial surface, a piece of enameled copper wire was used. The distal end of the wire was rolled into a coil 8 mm. in diameter, from one side of which the enamel was removed. The surface of the coil was flat and smooth. The coil was placed in the pericardial sac, resting lightly against the epicardium of the dorsal ventricular wall near the base of the heart. The shaft of this electrode was sutured firmly to the adjacent tissues. Electrocardiograms were taken by leading from electrodes placed on the dorsal and ventral epicardial surfaces and from an electrode in the ventricular cavity. A second set of curves was recorded after the ventral surface of the heart was covered with the pad soaked in Ringer's solution. A lesion was produced with the electrocoagulation unit. Thereafter, electrocardiograms were recorded in the manner and at the times designated in the legend of Fig. 8. Post-mortem examination revealed that the lesion involved the endocardial aspect of the entire ventral wall of the ventricle. Even the ridge of muscle which represents the primordial septum was burned. The apparent depth of the lesion was 1 mm.

The electrocardiograms recorded in Experiment 5 are reproduced in Fig. 8. After the subendocardial injury was produced, the changes in the QRS complexes of the leads from the dorsal and those of the leads from the ventral surface were opposite in character. Prior to the production of the injury, the QRS deflections had essentially the same form in leads of both kinds. A broad R wave was followed by an S wave of approximately equal amplitude. After the

injury, the complexes of the leads from the ventral epicardium consisted of a small Q wave followed by a broad R wave. The S wave had disappeared. The complexes recorded from the dorsal epicardial surface also underwent alterations in form. The R wave became narrower and the S wave broader and deeper.

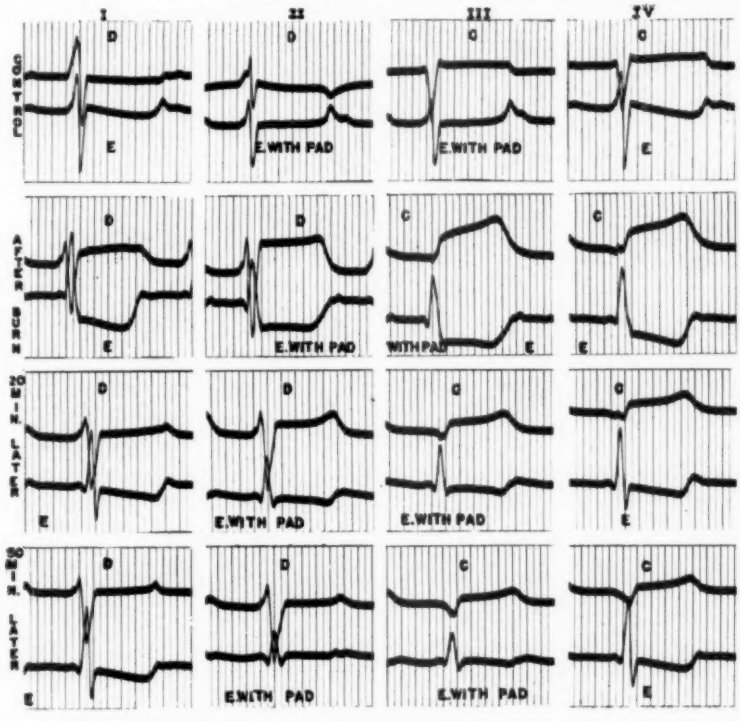

Fig. 8.—Upper curves in Columns I and II were recorded with the exploring electrode on or adjacent to the epicardial aspect of the dorsal ventricular wall (*D*); upper curves in Columns III and IV were recorded with the exploring electrode in the ventricular cavity (*C*). The lower curves were recorded with the exploring electrode on or adjacent to the epicardial aspect of the ventral wall of the heart (*E*). In Columns I and IV, the ventral surface of the heart was exposed to the air; in Columns II and III the ventral surface was covered with a pad soaked in Ringer's solution. Records were made at times indicated along left hand margin of figure.

Ordinate scale: in curves derived from ventricular cavity, 5 millivolts per centimeter; in curves derived from dorsal surface and from exposed ventral surface, 3 millivolts per centimeter; in curves derived from surface of pad covering ventral wall of heart, 0.5 millivolt per centimeter.

These electrocardiograms suggest delayed activation of the ventral wall of the heart. Changes in the QRS complexes similar in character and magnitude to those recorded in this instance were not encountered in any other experiment of this series. Their occurrence may have been due to the large extent of the endocardial lesion or to the involvement of some portion of the heart wall essential to rapid propagation of the wave of excitation.

The RS-T displacements recorded in Experiment 5 are readily perceptible. Subsequent to the production of the endocardial lesion, upward displacement was present in leads from the ventricular cavity and in leads from the dorsal

epicardium. When the exploring electrode was on the ventral epicardium and, therefore, on the opposite side of the injured layer, the displacement was downward.

These results afford evidence that the direction of the RS-T displacement produced by injury to the endocardial and subendocardial tissues depends primarily on the orientation of the lesion relative to the exploring electrode. The presence of uninjured muscle between the electrode and the lesion is significant in determining the direction of the displacement only when the uninjured myocardium underlying the exploring electrode constitutes one boundary of the injured region. In this case the electrode lies on that side of the lesion where the injury to the muscle is least. From an electrode so located, downward displacement of the RS-T segment will be an invariable derivative.

The results of Experiment 5 suggest also that upward displacement of the RS-T segment may be recorded in the absence of significant injury to the muscle cells underlying the electrode. For the appearance of upward RS-T displacement, it is necessary and sufficient that the exploring electrode face the side of the lesion on which the injury was most severe. In lesions produced by traumatizing the subepicardial layers, the region of most intense injury is also the most superficial. From an electrode placed on the surface of such a lesion, curves will be derived in which the RS-T displacement is upward. But when a lesion is produced by traumatizing the endocardial and subendocardial layers of muscle, the most severely injured cells are on that aspect of the lesion which faces the ventricular cavity. An electrode placed on the epicardial aspect of the opposite ventricular wall may lie within the electric field of that lesion at a point where the potential at the end of the QRS interval is positive enough to produce significant upward displacement of the RS-T segment.

If, in the electrocardiograms commonly recorded, subendocardial injury is attended more frequently by depression than by elevation of the RS-T segment, the explanation must be sought in the orientation of the injured muscle relative to the leads used. Such an explanation may be derived from concepts compatible with the dipole theory.

In an earlier investigation by one of us, in association with Barnes and Essex,[17] changes in the electrocardiogram induced by injuries confined to the endocardial and subendocardial tissues were recorded in a series of experiments on dogs. Extensive lesions were produced by mechanical means. The leads used were from an exploring electrode on the thoracic wall at a point overlying the injured region to an indifferent electrode on the right foreleg. Displacement of the RS-T segment was neither a consistent nor an impressive feature of the records obtained. The explanation of its absence remained obscure. In the present series of experiments, the production in dogs of lesions restricted to the endocardial tissues was not undertaken. We feel, however, that a brief discussion of this unsolved problem of the earlier investigation and its relation to the findings just reviewed is desirable.

The electric manifestations of cellular injury appear to be similar in turtles and dogs. In contrast, the spread of the wave of excitation is significantly different in the two species. In the heart of the turtle, no system of tissue special-

ized for the conduction of this wave has been identified. Its spread occurs ordinarily in the direction of a line pointing from the left basal to the right apical region of the ventricle.[11,13,16] Epicardial points are activated later than the endocardial points immediately underlying them. In the canine heart, a ventricular system for conducting the excitatory impulse is well developed. The entire endocardial aspect of the ventricular walls probably is activated almost simultaneously. The major portion of the QRS complex is formed while the wave of excitation is spreading across the wall from within outward. However, it appears unlikely that the course taken by this wave could influence portions of the electrocardiogram written after the impulse has completed its spread to all parts of the ventricular muscle. If valid, this principle would apply whether the heart under consideration was that of a dog or that of a turtle. Therefore, the effects of endocardial and subendocardial injury on the level of the RS-T junction and segment should not depend on the mode of propagation of the wave of excitation.

In all probability, the failure in the earlier experiments on dogs to record results similar to those subsequently obtained in turtles was dependent on some factor or factors other than the course pursued by the excitatory impulse. Two of these factors may be mentioned.

In the experiments on dogs, no effort was made to produce lesions so located that all of the resulting electric forces would have essentially the same orientation. In many of these experiments, the area of injury extended over the subendocardial muscle of the entire apical portion of the left ventricle including the septum. Under these circumstances the potential changes at a point on the thoracic wall overlying the lesion would represent the algebraic sum of electric forces of one kind from the injured region on one wall of the left ventricle and forces of inverse polarity from the injured region on the opposite wall. Because the traumatized muscle on the ventral side was nearer the exploring electrode than that on the dorsal side of the heart, the electric forces derived from the former perhaps should have been somewhat stronger than those derived from the latter. Without more detailed knowledge than is available, however, it is difficult to estimate what the net effect of combining the opposing forces might be.

It may also be pointed out that the lesions produced in the earlier experiments were not only large; they were also deep. In some places they extended through as much as a third of the thickness of the left ventricular wall. In the following section, the possible consequences of this circumstance on electrocardiograms derived by direct or indirect leads will be considered.

TRANSMURAL LESIONS

Early in the course of our experiments an attempt was made to conceive the sequence of electrocardiographic changes which would occur as a lesion was extended from the endocardium through the ventricular wall toward an electrode on the opposite epicardial surface. The diagram in Fig. 9 represents the concept reached. If the lesion initially involved only region *a*, and then was extended gradually to the size of region *c*, the negativity at the exploring electrode should

increase as the boundary of the injured zone advanced toward the surface. If, in the acute stage of lesion *c*, another lesion was produced on the epicardial side at *d*, the resulting positivity at the electrode due to the second lesion should cancel the negativity due to the first. The amount of RS-T displacement under these final circumstances should be slight. An attempt was made to perform an experiment in which such an extending lesion was created.

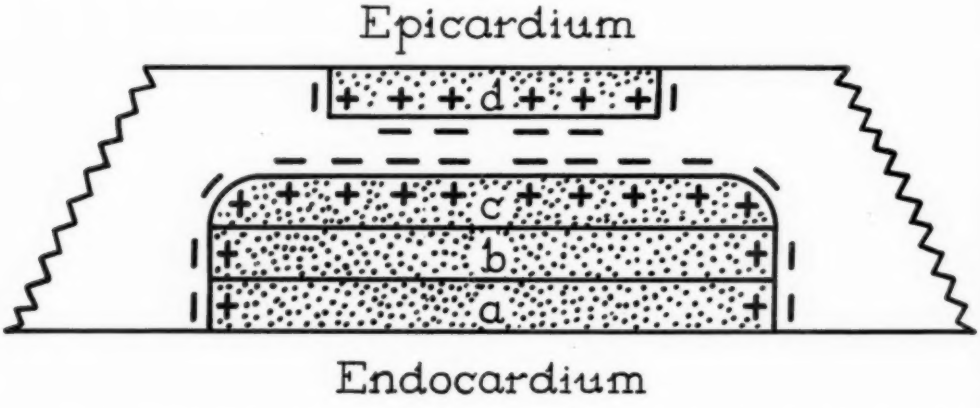

Fig. 9.—Diagrammatic representation of a lesion extending in stages *a*, *b*, and *c* from the endocardial toward the epicardial aspect of the heart wall; *d*, represents an injury to tissue at the epicardial aspect of the wall. For discussion, see text.

Experiment 6.—A small turtle was prepared in the usual manner. The filiform electrode was introduced into the left ventricular cavity. Electrocardiograms were recorded from the soft-tipped electrode resting on the epicardium of the ventral wall of the heart both before and after introduction of the filiform electrode into the ventricular cavity. Through the filiform electrode the electrocoagulating current was applied to the endocardial aspect of the ventral wall. The strength of the current and the duration of its flow were increased step by step. An electrocardiogram was recorded after each application of the current.

The soft-tipped electrode was then removed from the epicardial wall. With another electrode, a burn was made on the surface of the ventricle. This lesion overlaid but was smaller than the endocardial burn. The soft-tipped electrode was returned to its original position and a final electrocardiogram was recorded.

Post-mortem examination revealed that the endocardial burn was 7 mm. and the epicardial burn 4 mm. in diameter.

The electrocardiograms recorded in Experiment 6 are reproduced in Fig. 10. Only in those recorded immediately after the initial endocardial injury does the sequence of changes follow the anticipated course. Slight downward displacement of the RS-T segment is present in the curve labeled *C* in Fig. 10. In subsequent records, upward displacement of the RS-T segment is present and steadily increases. In those taken after the production of the epicardial lesion,

the RS-T segment does not become isoelectric but rises still higher to form curves of a monophasic type.

For this discrepancy between the predicted and the recorded results, there is a simple, if initially elusive, explanation. A zone of injured muscle across which a gradient of injury exists and from which a current of injury is derived

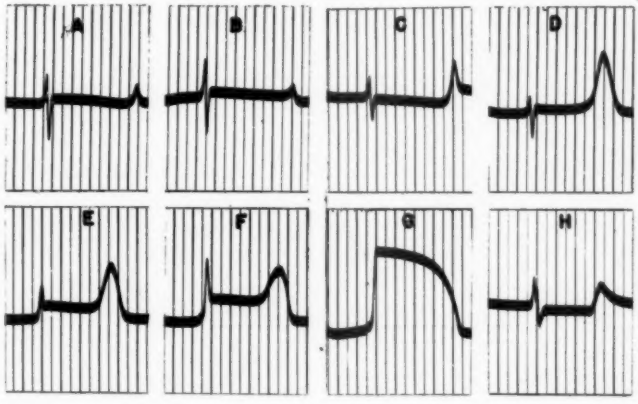

Fig. 10.—All curves except *H* were recorded with the electrode at the same point on the exposed portion of the ventral wall of the heart. *A*, Control; *B*, control after tip of electrode of the electrocoagulation unit had been introduced into the ventricular cavity; *C*, after making initial burn on endocardial aspect of ventral wall of heart at a point underlying the epicardial electrode; *D*, after second burn; *E*, after third burn; *F*, after fourth burn; *G*, after making small burn on the epicardial surface at a point overlying the endocardial burn; and *H*, epicardial electrode shifted onto uninjured muscle at right side of ventral wall of heart.

Ordinate scale uncertain, but approximately 3 millivolts per centimeter.

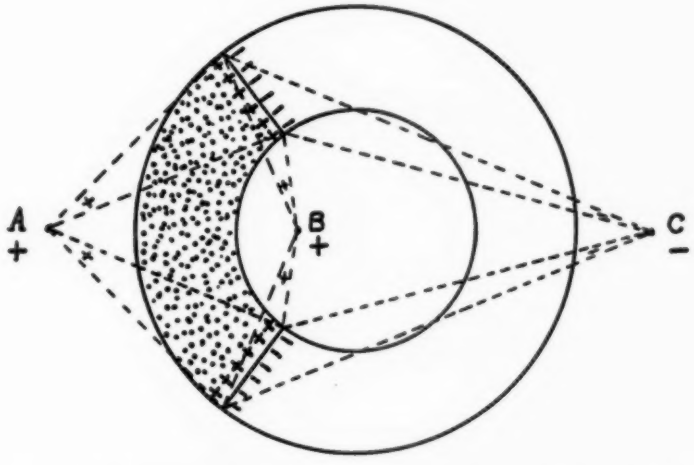

Fig. 11.—Diagrammatic representation of the electric field produced by an injury extending through the heart wall. This field is similar to one which would be produced if the injured muscle were polarized in the sense indicated. An electrode placed at a point adjacent to either the epicardial or endocardial aspect of the lesion would lie in a portion of the field where the potential was positive. An electrode placed at a point remote from the endocardial aspect of the lesion might lie in a portion of the field where the potential was negative.

lies just within the boundary between injured and uninjured muscle. In order to promote simplicity of description in the discussion which follows, the origin of the electric forces derived from an acutely injured muscle will be considered as located at this boundary. When an endocardial lesion is produced, a boundary of this kind is created, part of which is nearly parallel to the epicardial and endocardial surfaces, but there is another part which is more or less nearly perpendicular to these surfaces (Fig. 9). This latter part lies at the periphery of the lesion. Its breadth increases as the lesion is made deeper. During the inscription of the RS-T segment, the electric forces generated at this peripherally located boundary give rise to positivity at an exploring electrode placed on the epicardium at a point adjacent to the center of the lesion. These forces are opposed to those associated with the remaining parts of the boundary, which are parallel to the epicardial and endocardial surfaces. When the electrocardiograms reproduced in Fig. 10, *D* were recorded, the opposing forces apparently were of equal magnitude and the downward displacement of the RS-T segment present in the preceding electrocardiogram had disappeared. In the subsequent curves, the forces derived from the lateral aspects of the lesion apparently had a greater effect on the potential at the exploring electrode than those originating in the part of the boundary that was roughly parallel to the ventricular wall involved. With the production of the burn on the epicardium, another boundary parallel to the ventricular wall was created. Its orientation was such that the resulting forces opposed those associated with that portion of the boundary of the endocardial lesion which lay in a parallel plane. As a result, the forces produced at the peripheral portion of the boundary of the endocardial lesion gained the ascendancy and made the potential at the exploring electrode strongly positive. The RS-T segment was displaced upward and monophasic curves were recorded. A diagrammatic representation of this final stage is presented in Fig. 11.

Suppose that the distribution of boundaries defined in this diagram is an accurate representation of the situation which exists when an acute injury extends through the heart wall. Then an electrode placed on the endocardial surface of this transmural lesion should lie in a portion of its electric field where the potential is almost identical with that existing at an electrode placed on its epicardial surface. An experiment was designed to test this conclusion.

Experiment 7.—A large turtle was prepared in the usual manner. A lesion involving the endocardium on the left side of the ventricular cavity had been produced earlier in the experiment, but the electrocardiographic changes which had developed in the acute stage of that lesion had disappeared. The endocardial electrode was moved to the right side of the ventricular cavity and a set of electrocardiograms was recorded from the epicardial and endocardial electrodes. Through the endocardial electrode, the electrocoagulating current was applied in great strength for approximately five seconds. The white face of the burned tissue extended to the epicardium over an area 4 mm. in diameter. A series of electrocardiograms was recorded under circumstances described in the legend of Fig. 12.

Post-mortem examination revealed that the burn involved an area 8 mm. in diameter on the endocardial aspect of the wall of that portion of the ventricular cavity lying farthest to the right.

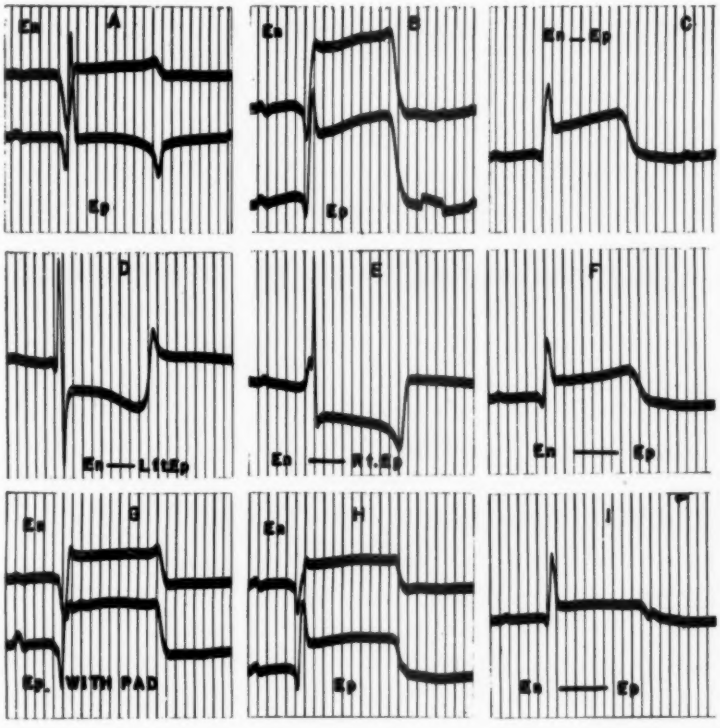

Fig. 12.—In all records where there are two curves, the upper one was derived from an electrode in the ventricular cavity (*En*) and the lower one from an electrode on the epicardial aspect of the right wide of the ventral wall of the heart (*Ep*). *A*, Control (ordinate scale: upper curve, 5 millivolts per centimeter; lower curve, 3.5 millivolts per centimeter); *B*, immediately after production of a burn extending from the endocardial to the epicardial aspect of the ventral wall of the heart on the right side, electrodes were in contact with the epicardial and endocardial aspects of the lesion (ordinate scale: upper curve, 2.5 millivolts per centimeter; lower curve, 3.5 millivolts per centimeter); *C*, epicardial electrode attached to left arm terminal of galvanometer and endocardial electrode to right arm terminal, lead selector set on Lead I (ordinate scale: 3.5 millivolts per centimeter); *D*, connections as in *C*, epicardial electrode moved onto uninjured muscle 8 mm. to left of lesion; *E*, connections as in *C*, epicardial electrode 3 mm. to right of lesion; *F*, epicardial electrode returned to site of lesion; *G*, pad soaked in Ringer's solution laid over ventral surface of heart, endocardial electrode on lesion and epicardial electrode on surface of pad at a point overlying the lesion (ordinate scale: upper curve, 2.5 millivolts per centimeter; lower curve, 1 millivolt per centimeter); *H*, pad removed from heart, endocardial and epicardial electrodes on respective surfaces of lesion (ordinate scale: both curves, 3.5 millivolts per centimeter); and *I*, connections, disposition of electrodes, and ordinate scales as in *C*.

The electrocardiograms recorded in Experiment 7 are reproduced in Fig. 12. They afford evidence that during inscription of the RS-T segment the potential was positive both at the epicardial and at the endocardial surface of the transmural lesion relative to the potential at a point remote from the heart. Covering the air-exposed portion of the ventral surface of the heart with a pad soaked in Ringer's solution produced certain changes in the electrocardiograms.

A reduction occurred in the amplitude of deflections recorded from the electrode placed on the surface of the pad at a point overlying the lesion. However, when the sensitivity was increased in that circuit in which the epicardial electrode was included, the curves recorded were quite similar to those obtained when the wick of the electrode rested on the surface of the lesion (Fig. 12, *G* and *H*).

The electrode on the epicardial surface of the lesion was attached to the left arm terminal and the electrode on the endocardial surface was attached to the right arm terminal of the same circuit. The lead selector switch was set on Lead I. The electrocardiograms reproduced in Fig. 12, *C* were then taken. With the connections described, the upward displacement of the RS-T segment indicates that the potential at the epicardial surface was positive relative to that at the endocardial surface. When the same connections were maintained and the epicardial electrode was moved off the surface of the lesion and onto uninjured muscle lying either to the right or to the left of the lesion, the potential at the epicardial electrode became negative relative to that at the endocardial electrode (Fig. 12, *D* and *E*).

These findings are compatible with those which would be anticipated if the significant electrical boundaries of the transmural lesion were disposed as is represented in Fig. 11. The fact that the potential of the epicardial surface of the lesion was positive to that of the endocardial surface rather than isopotential with it does not create a problem of significant proportions. In another experiment comparable to the one reported here, a lesion was produced which was less intense at the epicardial surface. The potential at the endocardial surface was then positive relative to that of the epicardium. The less pronounced positivity of the potential at the endocardial surface of the lesion in Experiment 7 was not the expression of a lesser intensity of injury on that aspect of the lesion. It may have been related to the complete desiccation of the tissues adjacent to the electrode with resultant alteration of the nature of the contact between the electrode and the cardiac surface.

A lesion extending through the ventricular wall from the epicardial to the endocardial surface has certain features in common with an infarct. In an attempt to define this relation more clearly, additional experiments were undertaken in which acute myocardial infarction was produced in dogs.

MYOCARDIAL INFARCTS

The chief characteristics of the electrocardiographic changes which commonly follow acute myocardial infarction either in man or in animals are well established. The explanation of these changes in terms of the dipole theory has been, on the whole, satisfactory and fruitful, but some perplexing problems presented by them are still unsolved. The facts indicate that a transmural infarct produces upward RS-T displacement in leads in which the exploring electrode faces the epicardial aspect of the involved wall. Changes of an inverse type are recorded in leads from an exploring electrode which faces the epicardial aspect of the uninvolved ventricular wall opposite the infarcted region. Thus, in infarction of the anterior apical portion of the left ventricle, upward RS-T dis-

placement occurs in electrocardiograms derived from an exploring electrode on a part of the thoracic wall which overlies the affected muscle. Such infarcts also commonly produce changes in the left arm potential, which result in upward RS-T displacement in leads from this extremity and in Lead I and downward displacement in Lead III. A unipolar lead from the left leg may show downward RS-T displacement. These changes which occur in anterior apical infarction are the inverse of those which develop during the acute stage of a posterior basal lesion.

The dilemma created by these findings has been defined by Bayley.[2] An acute subepicardial injury produces upward RS-T displacement in a lead from an exploring electrode which faces the affected portion of the ventricular wall. It is assumed that in this same lead an acute subendocardial injury would produce downward RS-T displacement. If the infarct is transmural and involves both the subepicardial and the subendocardial muscle, how then can the RS-T displacement so constantly associated with acute myocardial infarction develop? The problem becomes more perplexing if it is demonstrated that an infarct usually presents a more extensive surface on its endocardial than on its epicardial aspect. In the presence of such a lesion, the sum of the forces produced at the endocardial boundary would be greater than the sum of those produced at the epicardial boundary. Hence, downward RS-T displacement would be anticipated in a lead from an exploring electrode facing the epicardial surface of the infarct.

In his attempt to solve this problem, Bayley reviewed the studies of Mallory, White, and Salcedo-Salgar[14] and of Karsner and Dwyer[12] which concern the pathologic changes of myocardial infarction. Mallory and associates reported that a layer of subendocardial muscle 0.3 to 0.5 mm. in thickness is preserved in the infarcted region. Bayley reasoned that if, during the acute stage of myocardial infarction, the muscle fibers in this subendocardial layer retained the physiologic properties of uninjured cells, then a boundary between uninjured and injured muscle would persist in the subendocardial zone of the ventricular wall. Consequently, the forces contributed to the electric field by the infarct would have the same orientation as those produced by a lesion confined to the subepicardial myocardium. If a subendocardial muscle layer is invariably preserved over all the infarcted portion of the ventricular wall, the kind of RS-T displacement usually observed in cases of coronary occlusion is satisfactorily explained.

In our discussion of lesions extending outward from the endocardial to the epicardial surface of the heart of the turtle, an account was given of a discrepancy which arose between the electrocardiographic phenomena anticipated and those recorded when a transmural lesion was produced. In our experiments the subendocardial tissues were injured. Such trauma as occurred within the subepicardial zone was transmitted through the underlying layers of the myocardium. Upward RS-T displacement was recorded not only in unipolar leads from the endocardial surface but also in unipolar leads from the epicardial surface of transmural lesions. We have suggested that the site of origin of the electric forces which produced these electrocardiographic effects was the boundary between injured and uninjured tissue at the periphery of the lesion. Irre-

spective of the validity of this hypothesis, the fact remains that an electrode placed on the epicardial aspect of an acutely injured region extending completely through the heart wall lies at a point in the electric field of that lesion where the potential is positive during the inscription of the RS-T segment. Preservation of a subendocardial muscle layer is not essential to the production of this particular feature of the usual electrocardiographic changes associated with acute myocardial infarction.

Our observations do not prove that a boundary between injured and uninjured muscle does not persist in the subendocardial zone of a myocardial infarct. Experiments designed to record the potential variations at the endocardial surface of an acutely infarcted region offer an approach to this problem likely to contribute relevant and significant data. If, at this stage of infarction, a layer of subendocardial muscle is preserved in a functional as well as in an anatomic sense, an electrode placed on the endocardial surface of the infarct would be at a negative potential with respect to an indifferent reference point during the RS-T period. If the subendocardial cells are injured so severely that no significant gradient of injury exists in this region, then at the endocardial surface as at the epicardial surface a relatively positive potential would develop at the end of the QRS interval (Fig. 11).

An experiment designed to record the potential variations at a point on or near the endocardial surface of an infarct is readily conceived. Its execution is attended by certain difficulties. The usual procedure for recording the potential within the ventricular cavity entails the introduction of a sharp-tipped electrode through the ventricular wall. The position of the tip of such an electrode can be estimated by simple measures with reasonable accuracy. However, production of an injury with the electrode itself must be avoided if a significant record of the potential changes in the cavity is to be obtained. For this reason, the tip of the electrode must not be pressed firmly against the endocardial surface of the infarcted region, but should be placed in proximity to that surface. The distance of the electrode from the endocardial surface determines its position in the electric field of the injured muscle. If this distance is not too great, the electrocardiographic changes recorded should be similar to, though of lesser magnitude than, those which would occur if the exploring electrode were in contact with the inner surface of the lesion.

Method.—Dogs weighing between 10 and 12 kilograms were used in these experiments. Anesthesia was induced with morphine and urethane. The pericardium was exposed either by splitting the sternum or by resecting the fourth, fifth, and sometimes the sixth rib on the left side. The pericardial sac was incised and its margins were sutured to the thoracic wall. A major branch of the left coronary artery was ligated by passing a suture under the artery and its vena comitans. When only temporary occlusion of the artery was desired, a wire was included in the ligature and only a single knot was tied. Removal of the wire and release of traction on the thread restored the flow of blood.

In the initial experiments, records were taken with the Sanborn Tribeam electrocardiograph. In later experiments the Einthoven galvanometer was used.

Because of technical difficulties, satisfactory electrocardiograms were secured in only the last five of the nine experiments. The electrode used for obtaining records from the epicardium was the relatively nonpolarizable soft-tipped device already described. A similar electrode was placed in contact with the subcutaneous tissues of the left hind leg and this served as the reference point for this lead when the Einthoven galvanometer was used. The electrode introduced into the ventricular cavity was of the filiform type described in the account of the experiments on turtles. The tip of this electrode was thrust through the ventricular wall in a region supplied by the artery to be ligated. Its shaft was sutured firmly to some portion of the adjacent thoracic wall. This electrode was highly polarizable. Hence it was essential that the resistance of the circuit in which it was included should be high. For this reason, the cavity electrode was connected to the grid terminal of a vacuum tube amplifier and thus indirectly to the galvanometer. The indifferent electrode for cavity leads was a copper disk 2 cm. in diameter, which was placed in contact with the subcutaneous tissues of the left hind leg. When leads from the electrode on the epicardial surface to the electrode in the ventricular cavity were used, the former electrode was attached to the left arm terminal and the latter to the right arm terminal of the galvanometer. The lead selector switch was then set on Lead I.

Results.—The electrocardiograms reproduced in Figs. 13, 14, and 15 were taken with the Einthoven galvanometer. They were obtained in the course of an experiment which was not wholly satisfactory in certain respects. In the first place, ligation of the anterior descending branch of the left coronary artery at a point 2 cm. below the tip of the left auricular appendage did not produce pronounced displacement of the RS-T segment either in the lead from the epicardial or in that from the endocardial side of a part of the ventral ventricular wall apparently supplied by this vessel. Only after ligation of the terminal branches of the circumflex division of the left coronary artery (Fig. 16) did more striking displacement of the RS-T segment develop. Secondly, because the region of infarction included only a limited portion of the myocardium at the apex of the left ventricle, the first electrode introduced into the left ventricular cavity did not lie opposite the center of the injured region. A second electrode, therefore, was introduced into this cavity at a point more centrally located relative to the infarct, but this was done only after the coronary vessels had been ligated and the resulting electrocardiographic changes had already developed.

In other respects the experiment was satisfactory. At the end of it, the heart was opened and the tips of both electrodes that had been introduced through the ventricular wall were observed to lie within the cavity of the left ventricle. The first electrode extended into this cavity a distance of 8 mm. and the second, a distance of 4 millimeters. A small thrombus 3 mm. in diameter had formed around that portion of each electrode which projected beyond the inner surface of the ventricular wall. Except at the points of entrance, no gross endocardial injury produced by the electrodes could be identified.

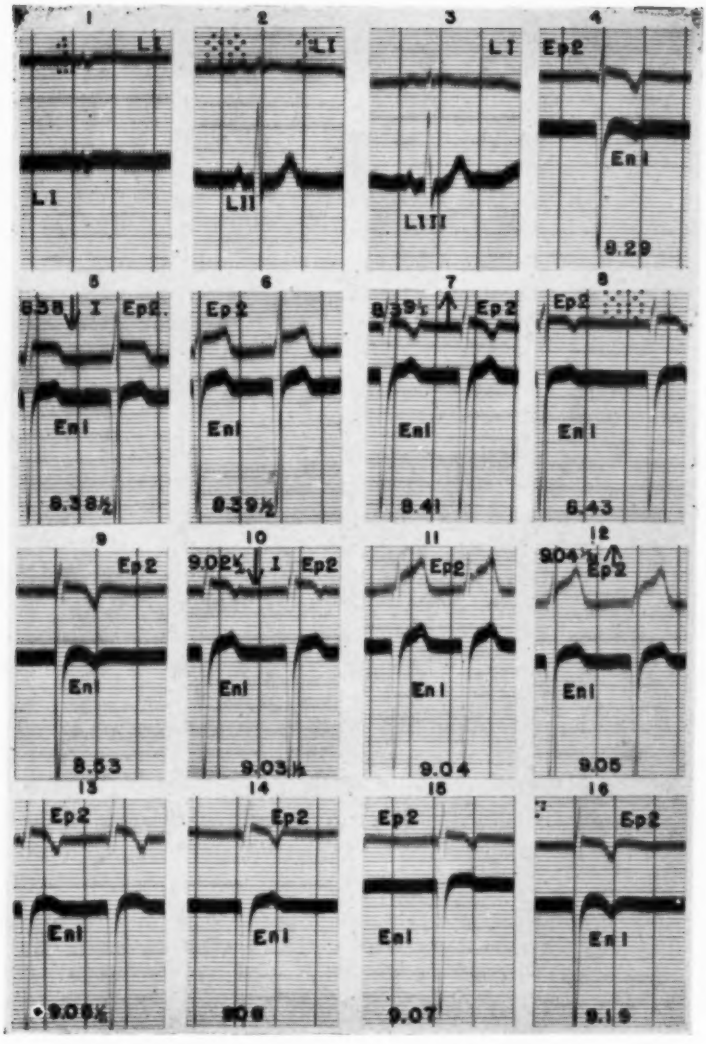

Fig. 13.—Ordinate scale: in standard limb leads, 1 millivolt per centimeter; in direct leads from ventricular surface or cavity, 20 millivolts per centimeter.

Curve	Time	Upper curve Site of epicardial electrode	Lower curve Site of endocardial electrode
1	8:00	Lead I	Lead I
2	8:02	Lead I	Lead II
3	8:04	Lead I	Lead III
4	8:29	Point 2 (see Fig. 16)	Point 1
	8:38 Occlusion at I (see Fig. 16) for 90 seconds		
5	8:38½	Point 2	Point 1
6	8:39½	Point 2	Point 1
7	8:41	Point 2	Point 1
8	8:43	Point 2	Point 1
9	8:53	Point 2	Point 1
	9:02½ Occlusion at I for 105 seconds		
10	9:03½	Point 2	Point 1
11	9:04	Point 2	Point 1
12	9:05	Point 2	Point 1
13	9:05½	Point 2	Point 1
14	9:06	Point 2	Point 1
15	9:07	Point 2	Point 1
16	9:19	Point 2	Point 1

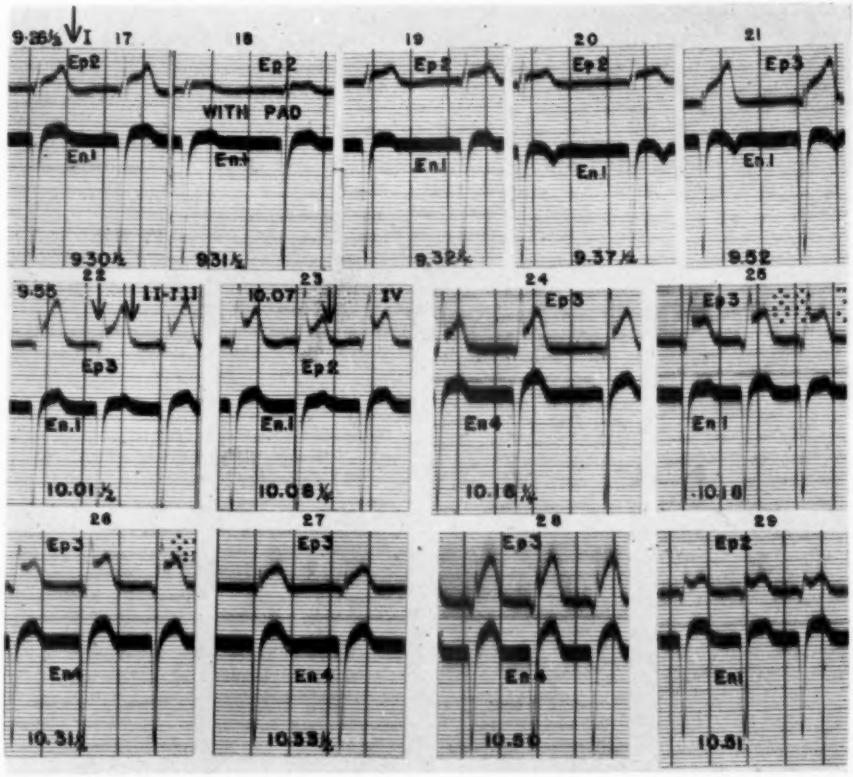

Fig. 14.—Ordinate scale: 20 millivolts per centimeter.

Curve	Time	Upper curve Site of epicardial electrode	Lower curve Site of endocardial electrode
	9:26½	Occlusion at I (see Fig. 16) permanently	
17	9:30½	Point 2 (see Fig. 16)	Point 1
18	9:31½	Point 2 with pad	Point 1
19	9:32¼	Point 2	Point 1
20	9:37½	Point 2	Point 1
21	9:52	Point 3	Point 1
	9:55	Occlusion at II and III permanently	
22	10:01½	Point 3	Point 1
	10:07	Occlusion at IV permanently	
23	10:08¼	Point 2	Point 1
24	10:16¼	Point 3	Point 4
25	10:18	Point 3	Point 1
26	10:31½	Point 3	Point 4
27	10:33½	Point 3 with pad	Point 4
28	10:50	Point 3	Point 4
29	10:51	Point 2	Point 1

Analysis of the electrocardiograms in Figs. 13, 14, and 15 should not be extended to exact quantitative determinations. After the first of the standard limb leads had been taken, the sensitivity of the galvanometer was readjusted and it was not altered again throughout the remainder of the experiment. It should be recognized, however, that other factors affected the magnitude of the

deflections in the electrocardiograms taken. The electrode on the endocardial aspect of the lesion probably was not in contact with the ventricular wall. The distance of this electrode from the endocardium may have varied during the contraction of the ventricle and as a result of the rhythmic inflation and deflation of the lungs. The size of the deflections in leads from the epicardial electrode was reduced whenever a small amount of free fluid accumulated about

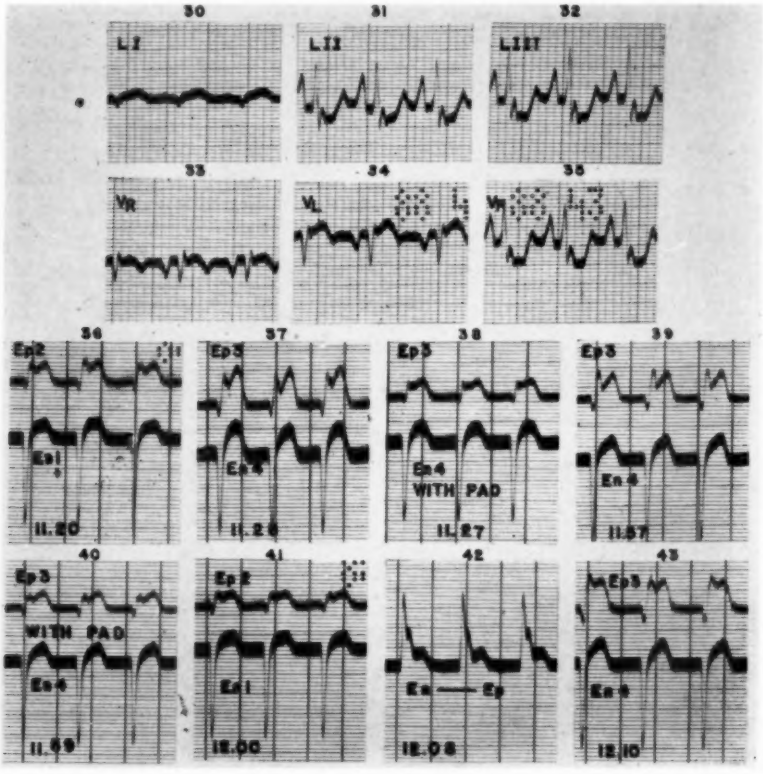

Fig. 15.—Ordinate scale: in standard limb leads, 1 millivolt per centimeter; in direct leads from ventricular surface or cavity, 20 millivolts per centimeter.

Curve	Time	Upper curve Site of epicardial electrode	Lower curve Site of endocardial electrode
30		Lead I	
31	10:55	Lead II	
32		Lead III	
33		Unipolar lead, right foreleg	
34	11:05	Unipolar lead, left foreleg	
35		Unipolar lead, left hindleg	
36	11:20	Point 2 (see Fig. 16)	Point 1
37	11:25	Point 3	Point 4
38	11:27	Point 3 with pad	Point 4
39	11:57	Point 3	Point 4
40	11:59	Point 3 with pad	Point 4
41	12:00	Point 2	Point 1
42	12:08	L. A. terminal at epicardial point 3; R. A. at endocardial point 4	
43	12:10	Point 3	Point 4

the tip of this electrode. Therefore, while the magnitude of the RS-T displacement in the electrocardiograms of this series is of some interest, we shall emphasize only its direction, which is of greater significance.

Fig. 16.—Diagram of heart indicating points to which reference is made in legends of Figs. 13, 14, and 15.

In Fig. 13, curves 5 to 9, are represented the electrocardiographic changes associated with, and sequential to, temporary occlusion of the anterior descending branch of the left coronary artery. During this initial procedure the occlusion was maintained for ninety seconds. Upward displacement of the RS-T segment developed in leads from the electrode placed on the epicardium. The magnitude of this displacement was not great. In leads from the endocardial electrode, the inverted T wave became upright and this change was accompanied by a slight upward shift in the RS-T level. These phenomena appeared within thirty seconds after occlusion of the artery and regressed with almost equal speed.

Twenty-four minutes after the first occlusion of the artery, traction was again placed on the ligature and was maintained on this occasion for 105 seconds (Fig. 13, curves 10 to 16). The changes during this period of ischemia were slightly more pronounced in leads from both the epicardial and the endocardial electrodes. In other respects, the developments were like those which followed the initial occlusion.

Twenty-four minutes later the ligature was tied permanently (Fig. 14, curve 17). The electrocardiographic changes which appeared during the first few minutes after this occlusion simulated those occurring in the preliminary periods of ischemia. However, after five minutes there was some decrease of the upward displacement of the RS-T segment in leads from both the epicardial and endocardial electrodes, particularly in the latter (Fig. 14, curve 19). In the

records made twenty-six minutes after the permanent occlusion (Fig. 14, curve 21), the epicardial electrode was shifted to a point nearer the center of the injured region; the position of the endocardial electrode was not changed.

Twenty-nine minutes after the final ligature had been placed on the anterior descending branch of the left coronary artery, the first of the terminal branches of the left circumflex artery was occluded (Fig. 14, curve 22). Twelve minutes later, the third and last ligature was placed around one of these branches (Fig. 14, curve 23). Fifty minutes after the first permanent occlusion, an electrode was introduced into the left ventricular cavity at a point near the center of the injured myocardium and an electrocardiogram was recorded from this lead (Fig. 14, curve 24). Between ninety and 120 minutes after the first permanent occlusion, the degree of elevation of the RS-T segment was maximal in both the epicardial and the cavity leads. It was at this time when the potential at two points on the endocardial aspect of the injured muscle was positive during inscription of the RS-T segment that the standard limb leads and the unipolar extremity leads were recorded. The presence of downward displacement of the RS-T segment in the unipolar lead from the left hind leg at a time when cavity leads displayed upward RS-T displacement is of particular interest.

One of the last electrocardiograms in the series (Fig. 15, curve 42) records the potential difference between the electrode placed near the center of the epicardial aspect of the infarcted tissue and an electrode in the ventricular cavity 3 or 4 mm. from the inner surface of the same part of the infarct. The upward displacement of the RS-T segment in this lead indicates relative positivity of the epicardial electrode at the end of the QRS interval. However, the degree of positivity of the epicardial relative to the endocardial electrode was less than the degree of positivity of the epicardial electrode relative to an electrode placed at a point remote from the heart (Fig. 15, curve 43).

Finally, attention may be directed to one other observation which concerns the magnitude rather than the kind of electrocardiographic alterations which developed. In many of the curves reproduced in Figs. 13, 14, and 15, electrical alternans is present. This phenomenon is most obvious in curve 23 of Fig. 14. Examination of these curves reveals that when upward displacement of the RS-T segment was greater in the epicardial electrocardiogram, it was likewise greater in the lead from the endocardial electrode. If the electric forces responsible for this displacement arose at a boundary which lay between the epicardial and endocardial surfaces, greater positivity on one side of the ventricular wall should have been accompanied by greater negativity on the other. If, on the other hand, the electric forces in question originated at the periphery of the lesion, an increase in their magnitude would have a similar effect on the potential of both surfaces of the ventricular wall and, therefore, on that of both electrodes.

The observations presented here illustrate a series of experiments which was incomplete. In particular, studies should have been made of the changes of potential within the left ventricular cavity following ligation of the circumflex branch of the left coronary artery. One attempt to do this was made but the results of this experiment could not be interpreted precisely because of inadequate information regarding the position of the endocardial electrode.

In summary of the available data on the electrocardiographic effects of experimental myocardial infarction, the following statements may be made. In experiments on dogs, the artery or arteries supplying the anterior apical portion of the left ventricle were ligated and the potential changes within the left ventricular cavity were recorded. The tip of the exploring electrode was placed in this cavity at a point near the center of the injured region of the adjacent myocardial wall. During the RS-T interval, the potential at the tip of the cavity electrode was positive relative to the potential at an electrode placed at a point remote from the heart. This positivity at the endocardial aspect of the lesion existed in the presence of changes typical of anterior apical infarction in leads from the epicardial surface of the lesion, in the standard limb leads, and in the unipolar extremity leads.

The results of our experiments do not justify the conclusion that the electric forces responsible for RS-T displacement in acute myocardial infarction always arise at boundaries which define the peripheral limits of the lesion. We may add that the application of concepts derived from experiments in which the blood supply of some part of the healthy canine myocardium was suddenly cut off to the interpretation of what takes place when the nutrition of the human heart is disturbed by thrombosis of one of its sclerotic arteries must always be accomplished with due regard for the possibility of error. To assume that the results of our experiments can be applied to all cases of myocardial infarction in man would be premature.

Having accorded these considerations the recognition which they merit, we may make the following statements without elaboration of their implications. A boundary between injured and uninjured muscle must define all or part of the peripheral limits of every myocardial infarct. Since the left ventricle is conical and since extension of a zone of infarction to its basal border would not produce a junction between injured and uninjured muscle in this region, the combined areas of the apical and basal boundaries of the infarct may be small in comparison with the areas of its other boundaries. In a heart which is not dilated, the area of the boundaries at the periphery of the infarct may approach the area of the endocardial aspect of the injured tissue. This would be most likely to happen during ventricular systole. At this time, the size of the ventricular cavity is decreased and the thickness of the ventricular walls is increased. It is during systole that the RS-T segment is inscribed.

SUMMARY AND CONCLUSIONS

The modifications of the RS-T segment of the ventricular complex produced by acute lesions of various types were recorded in a series of experiments on turtles and dogs.

In experiments on turtles, it was found that when the ventral surface of the heart was exposed to air an acute injury involving only the outer layers of the exposed ventricular wall produced upward RS-T displacement in unipolar leads from the epicardial surface of the affected region but, as a rule, did not produce downward RS-T displacement in leads from an adjacent portion of the ven-

tricular cavity. Downward RS-T displacement did occur in such cavity leads when the ventral epicardial surface was in contact with a conducting medium.

When a lesion involved the same part of the ventricular wall but was confined to the subendocardial muscle layers, the RS-T displacement was upward in leads recorded from an adjacent part of the ventricular cavity and in leads from the epicardial aspect of the ventricular wall opposite the damaged portion of the myocardium. RS-T displacement was downward when the exploring electrode was placed on the epicardial aspect of the affected ventricular wall.

When, in experiments on turtles, a lesion involving both the inner and outer layers of the ventricular wall was produced by electrocoagulation, upward RS-T displacement was recorded in leads from either the epicardial or the endocardial aspect of the region of injury. Similarly, when acute myocardial infarction was produced in the anterior apical portion of the canine heart by coronary ligation, the RS-T displacement was upward in leads from a portion of the ventricular cavity adjacent to the injured muscle and in curves recorded with the electrode on the epicardial surface of the region of infarction. The electric forces responsible for upward RS-T displacement on both aspects of these transmural lesions were attributed to the boundaries between injured and uninjured muscle at the peripheral margins of the lesion.

Muscle juice, probably because of its high potassium content, produces maximal RS-T displacement when it is placed on the ventricular surface.

An attempt has been made to interpret these observations in terms of the dipole theory as it applies to the electrocardiographic consequences of acute myocardial injuries.

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THE VARIED CLINICAL SYNDROMES PRODUCED BY DISSECTING ANEURYSM

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A GENERATION ago when Herrick[1-3] and Levine and Tranter[4] first reported their fundamental observations in acute thrombosis of the coronary arteries, the ante-mortem diagnosis of myocardial infarction was a medical rarity. Today myocardial infarction is a medical condition readily recognized by most physicians. We believe a somewhat analagous situation exists with reference to the diagnosis of dissecting aneurysm of the aorta. The various clinical syndromes produced by this disturbance are gradually becoming clarified. Physicians are not only beginning to recognize the condition in patients who do not survive, but are suspecting its presence in patients who have survived the accident and recovered.

Willius and Cragg[5] listed as reasons for the failure to make the diagnosis of dissecting aneurysm: (1) The relative infrequency of the condition; (2) the absence of a characteristic syndrome; (3) the limitation of special diagnostic adjuncts; and (4) universal lack of clinical suspicion. We feel the last of these is perhaps the most important. There has been an increase in accurate diagnosis during the past decade, but Reich[6] has stated that "it is only through relentless correlation of post-mortem findings with the clinical picture in individual cases, that a true clinical consciousness of the disease can be adequately established."

In the forty-four cases that are the basis of this report (eleven were diagnosed ante mortem), an attempt will be made to emphasize some of the features that should enable one to make a clinical diagnosis of dissecting aneurysm.

CLINICAL FEATURES

Incidence.—Until we learn to recognize recovered cases of dissecting aneurysm, we will not be able to arrive at an approximation of the true incidence of dissecting aneurysm. We have seen at least two cases that we feel are instances of healed dissecting aneurysm. Weiss and co-workers[7] believed that one out of ten patients recover, and die of other causes. This was found to be the case in two of our cases at necropsy.

Mote and Carr,[8] in a five-year study from the coroner's office in San Francisco, found that 1.1 per cent of all cases of sudden death were due to dissecting aneurysm. They emphasized that there was a greater incidence in coroners'

From the Philadelphia General Hospital and the Jewish Hospital.
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offices than hospital records would indicate, because death might be so sudden that hospitalization was not possible. Gouley[9] has found dissecting aneurysm to be one of the commoner causes of sudden death in Philadelphia. He found the incidence to be one in every 480 autopsies on patients beyond the age of 20 years.[10] Glendy and associates[11] found nineteen cases in 8,200 autopsies at the Massachusetts General Hospital over a thirty-eight-year period, an incidence of one in every 431 autopsies.

Age and Sex.—Interest in dissecting aneurysm of the aorta was stimulated by the excellent monograph written by Shennan[12] in 1933. He added seventy-five instances of dissecting aneurysm collected throughout England to those already reported, making a total of 302 proven cases. Over 80 per cent of these occurred in subjects over 50 years of age; 65 per cent were in men. A similar incidence is found in the forty-four cases we are reporting (Table I). They ranged in age from 35 to 82 years, with the majority occurring in the fifth and sixth decades. Of the forty-four cases, 67 per cent were in men. This experience conforms to the generally accepted opinion concerning the age and sex incidence of dissecting aneurysm. However, attention must be paid to the data presented by Schnikter and Bayer.[13] In reviewing the literature up to 1943, they were impressed with the occurrence of this condition in younger people. In the 580 cases they accepted as proven cases of dissecting aneurysm gathered from the world's literature, 141, or 24 per cent, occurred in individuals less than 40 years of age. Of those cases occurring in women, approximately 50 per cent were seen during pregnancy.

TABLE I. AGE AND SEX INCIDENCE OF DISSECTING ANEURYSM

AGE	SEX		TOTAL	
	MALE	FEMALE	NUMBER	PER CENT
30–39		2	2	4.5
40–49	3	1	4	9.0
50–59	12	4	16	36.3
60–69	10	3	13	29.8
70–79	3	4	7	15.9
80–89	1	1	2	4.5
	29	15	44	

Symptomatology.—Many observers[6,7,11-16] have published excellent clinical descriptions of the symptoms encountered. As a rule the patient is suddenly seized with a severe tearing or ripping pain in the chest or precordial area, or upper abdomen. Collapse, sudden unconsciousness, or death may then ensue. If consciousness is retained, the pain may increase greatly in intensity. It may

radiate to the shoulder, back, abdomen, renal area, or groin. The radiation of the pain will depend to some extent on the direction of the dissection, and the various organs involved. The time relations of the various types of pain may be of help in the differential diagnosis of dissecting aneurysm. The pain may be so intense that repeated injections of narcotics fail to give relief. In many cases, however, there may be no history of pain whatsoever. There have been reported[11,13,17,18] cases in which pain was absent during the entire course of the illness. In twenty-four of our forty-four cases there was no recorded history of pain at any time during the patient's illness (Fig. 1).

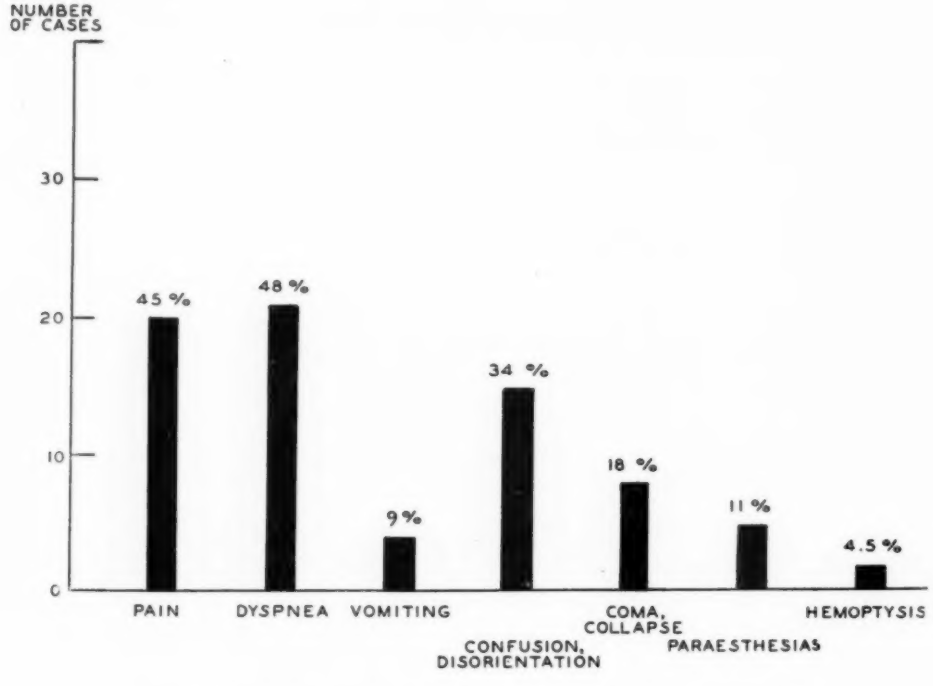

Fig. 1.—Symptomatology in forty-four cases of dissecting aneurysm.

Dyspnea was also an important symptom. It is understandable why so many cases, particularly those occurring in older individuals, with dyspnea and without pain are considered cardiac in origin and are not recognized as cases of dissecting aneurysm.

We were impressed with the number of times that neurological disturbances played a large part in the symptomatology. The shock occurring with the tearing of the aorta may be so severe that syncope or collapse develops. In some cases, the only history obtainable was that the patient was found in coma. In other instances agitation, disorientation, convulsive seizures, or bizarre peripheral neurological signs may cause one to look to the cerebrum or spinal cord as the primary source of the trouble.

Physical Findings.—The physical findings will vary greatly, depending upon the length of time the patient survives, the age of the patient, the preexisting cardiovascular disturbance, and the vessels and organs involved in the dissection. If the patient survives the initial aortic tear, fever, tachycardia, and tachypnea usually develop (Fig. 2).

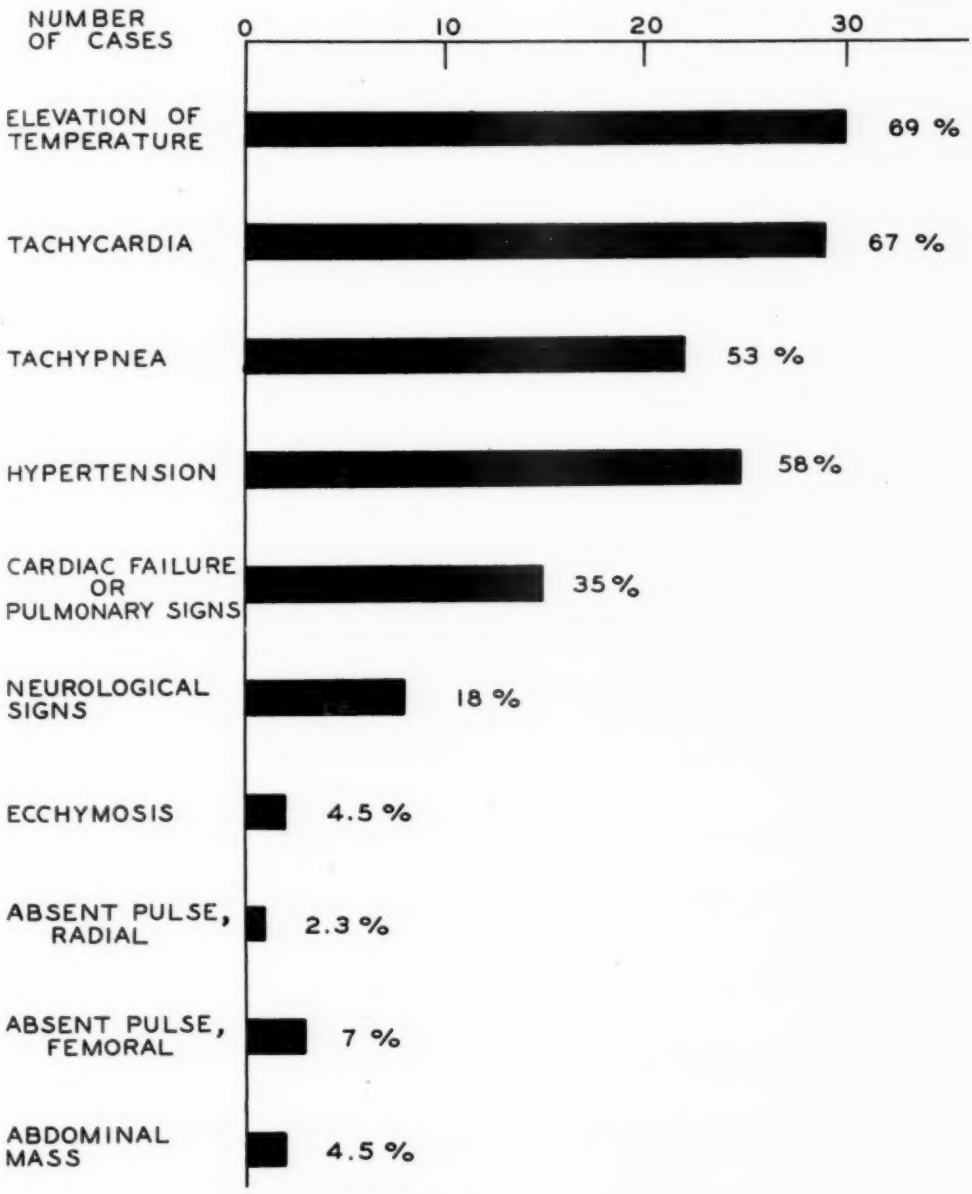

Fig. 2.—Physical findings in forty-four cases.

Hypertension is frequently present, but the question of the hypertensive background of dissecting aneurysm is still quite controversial. Mote and Carr,[8] Schnikter and Bayer,[13] Hamburger and Ferris,[17] and Rogers[19] have all stated that there may be no history of hypertension. In the forty cases in which a blood pressure was recorded in our series, systolic pressures of 150 mm. Hg or more were found in twenty-five instances. Systolic pressures ranged from 70 to 300 mm. Hg, and in one case the pressure was 130 mm. higher in the right than in the left arm. Diastolic pressures ranged from 30 to 130 mm. of mercury. A few cases with hypotension developed hypertension before they died, but the reverse also occurred. It is, of course, quite possible that some patients with low or normal pressures on admission had hypertension before aortic rupture occurred. There seems no question, however, that some cases, particularly those in younger individuals, fail to present evidence of hypertension in the history or physical examination or at necropsy.

Cardiac enlargement, signs of cardiac failure, various cardiac murmurs, gallop rhythm, or a pericardial rub may all be found (Table II). It is these signs particularly that direct our attention toward the heart, suggesting the diagnosis of cardiac failure or myocardial infarction rather than dissecting aneurysm.

One important sign that may be almost pathognomonic of dissecting aneurysm is the development of the diastolic murmur of aortic regurgitation. Gouley and Anderson,[10] Resnik and Keefer,[20] Hamman and Apperly,[21] Zimmerman,[22] and Wainwright[23] have all called attention to this finding, particularly in chronic cases. The murmur is apparently due to dilatation or deformity of the aortic ring, resulting from the dissection. When sought for diligently, its discovery may enable one to make the diagnosis in suspected cases.

TABLE II. CARDIAC FINDINGS RECORDED IN FORTY-FOUR CASES

Cardiac enlargement		8
Gallop		2
Friction rub		2
Auricular fibrillation		2
Murmurs	Aortic systolic	10
	Aortic diastolic	6
	Mitral systolic	12
	Mitral diastolic	4

Signs of cardiac failure, pulmonary consolidation, or pleural effusion occurred in fifteen cases. These signs were usually more marked in the left hemothorax. On five occasions bloody pleural fluid was obtained on aspiration.

Some of the most bizarre findings are those suggestive of neurological involvement. Particular attention has been paid to this topic by Niehaus and

Wright,[18] Rogers,[19] and Weisman and Adams.[24] Patchy and bizarre vascular or neurological findings may be obtained with or without pain. These varied signs, most marked as a rule in the legs, are due to the circulatory deficiencies resulting from involvement of the intercostal, lumbar, or femoral arteries. The dissection may produce a periarterial sympathectomy. Or involvement of an anterior spinal artery may result in a sudden painless paraplegia. Weisman and Adams[24] made a detailed study of the neurological findings in thirty-eight cases of dissecting aneurysm. The diagnostic accuracy was greatly increased in those cases in which the neurological findings predominated.

Laboratory Findings.—Many of the patients did not live long enough for detailed laboratory studies to be made. Leucocytosis was a frequent finding, with an increase particularly in the polymorphonuclear leucocytes. If the bleeding (into the aorta, pericardium, or pleura) is extensive enough, severe progressive anemia may develop in a few hours. The urine may show a trace to a cloud of albumin. If dissection has approached or involved the renal arteries, hematuria or even uremia may predominate in the symptom complex.

Electrocardiograms were available for study in twenty-three cases. It is difficult to evaluate the changes found. This is particularly so when we realize that the major portion of these individuals usually had severe vascular disease before their dissecting aneurysm developed. Many previously had had one or more myocardial infarctions. It would be expected, therefore, to find abnormal electrocardiograms in most of these patients. Changes of the QRS complex, S-T segment, and T waves were present in almost all of the tracings. The changes, however, were not specific enough to consider the electrocardiogram as diagnostic of dissecting aneurysm. In three of our cases, patterns suggestive of acute myocardial infarction were obtained. At necropsy, myocardial infarcts due to involvement of the coronary arteries by the aortic dissection were found. A number of authors have reported cases in which the electrocardiograms resembled those found in acute myocardial infarction, without an infarct being demonstrable post mortem. In one of our cases, an electrocardiogram indicative of acute pericarditis, plus a bloody pericardial tap, led to an ante-mortem diagnosis of dissecting aneurysm. By and large, however, the electrocardiographic changes are nonspecific and merely indicate the presence of some myocardial or pericardial derangement.

Roentgen examination may also be of some help in the differential diagnosis. Wood and associates[25] have described these signs in detail. They consist of deformity of the aortic or supracardiac shadow. This may gradually or rapidly increase in size. In Case 9, for example, gradual progressive increase in the size of the aorta over a period of one year was the sign which led one of our colleagues to make a diagnosis of dissecting aneurysm of the aorta months before death ensued.

Pathologic Aspects.—Discussion of the various pathologic features underlying dissecting aneurysm of the aorta have been published by Shennan,[12] Moritz,[26] Klotz and Simpson,[27] Schattenberg and Ziskind,[28] Leary and Weiss,[29] and Sailer.[30] Readers are referred to these articles for detailed consideration of

the pathologic features of dissecting aneurysm. Some authors continue to adhere to the theory that rupture begins in the intima at or close to the margin of an atheromatous ulcer. The pressure of the column of blood then is supposed to carry the dissection into and along the media. Peery[31] has described an incomplete tear of the aorta that he thought might be the possible precursor of dissecting aneurysm.

Most observers, however, describe the process somewhat as follows: The primary change in the aorta is a cystic degeneration of the media (so-called Erdheim's medionecrosis cystica). The cause of this degeneration is not certain. In this type of aorta, there occurs a rupture of one or more medial nutrient vessels into one of the cystic spaces, producing a hematoma. The hematoma enlarges, splitting the layers of the media, and the intima is then secondarily torn. An opening is thus made into which the large aortic column of blood may force itself and produce varying degrees of dissection along the medial coat. The dissection, which begins in the ascending aorta in over 70 per cent of the cases, may also extend cuspward. Some writers feel that dissection backward toward the cusps is responsible for distortion of the aortic ring and the resultant diastolic murmur that is such a valuable diagnostic sign.

An additional pathologic finding that occasionally may be the basis of dissection is hypoplasia or coarctation of the aorta. Schnikter and Bayer[13] and Reifenstein and associates[32] in particular have discussed this. Schnikter and Bayer[13] suggested that if dissecting aneurysm occurred in individuals before the age of 40 years, there was a strong probability that hypoplasia or coarctation of the aorta would be found at necropsy. They cited Maude Abbott's statistics, in which thirty-three of her 200 cases of coarctation of the aorta died of dissecting aneurysm.

Irrespective of the pathologic basis of the dissection, the length of time that the patient survives after the initial catastrophe will determine the further clinical and pathologic findings. The shock may be so severe that death is instantaneous. Or the progress of the dissection may be slower, and the process advance along the aorta. If the great vessels arising from the arch are involved, cerebral symptoms may predominate; or the dissection may involve the spinal arteries, yielding an "anterior spinal artery thrombosis syndrome." Beyond this the gastrointestinal vessels may be involved, and gangrene of the bowel or mesenteric thrombosis ensue. Frequently, one or the other renal artery is involved, and hematuria or renal infarction results. In an occasional case the entire abdominal aorta has been involved, so that at necropsy the basis of a saddle or femoral thrombosis with gangrene of the leg was found to be a dissecting aneurysm beginning in the thoracic or abdominal aorta.

If death does not result from shock, the terminal event is most apt to be rupture into the pericardium. In other instances, rupture may be into the pleural cavity, particularly the left. In an occasional case, especially one lasting for sometime, death may be due to cardiac failure. As a matter of fact, this was the mode of death in almost 50 per cent of the sixty-six cases listed as "chronic dissecting aneurysm" by Shennan.[12]

We must not lose sight of the fact that dissecting aneurysm is not invariably fatal. Weiss[7] felt that one out of ten cases of dissecting aneurysm heal, and that "dissecting aneurysm of the aorta may be compatible with good health for many years, and death result from other causes." A number of cases[7,16] have been reported in which dissection resulted in a double-barrelled aorta. The patients lived long enough to develop deep atheromatous changes in the new aortic wall. This occurred in two of our cases.

DISCUSSION

As interest in the question of dissecting aneurysm increased, hospital necropsy records[33] and individual reports[34-40] of verified cases diagnosed ante-mortem accumulated. It became apparent that the condition was neither as rare nor as difficult to diagnose as it was first considered to be. We have not attempted to completely review all the pertinent literature; extensive bibliographies can be found in a number of papers. To date there must be almost 650 cases on record, including those reported in this presentation. Whereas, in only six of Shennan's 302 cases was the diagnosis suspected before death, with the eleven cases that we are including there are reports of at least sixty cases which were diagnosed clinically.

We have attempted to correlate the various clinical and pathologic studies reported with the findings in our cases. Depending on the group of symptoms presented, dissecting aneurysms that do not produce sudden death can be divided roughly into the following five clinical types.

Cardiovascular.—This is by far the largest and most important group. In nineteen of our forty-four cases, the primary ante-mortem diagnosis referred to the cardiovascular system (Table III). They were considered as cases of hypertensive or arteriosclerotic heart disease, or simply cardiac failure. Acute myocardial infarction was diagnosed in four cases, and considered as a possibility in four of the eleven cases diagnosed correctly. This difficulty in differential diagnosis is quite understandable. Hypertension, chest pain, evidence of cardiac failure, a pericardial friction rub, or the various physical signs of cardiac involvement previously referred to all contribute to a diagnosis of hypertension, cardiac failure, or acute myocardial infarction. In cases of "chronic dissecting aneurysm," as discussed by Gouley and Anderson[10] and Shennan,[12] marked cardiac enlargement may result. Finally, intractable cardiac failure may occur, and little basis remain for venturing a diagnosis of dissecting aneurysm.

In an occasional case, the clinical picture may closely simulate primary iliac or femoral thrombosis and little attention be given to the possibility of an underlying thoracic or abdominal dissecting aneurysm.

Cerebral.—In ten of our cases the final ante-mortem diagnosis was cerebral vascular accident. We have already referred to the importance of the cerebral and neurological findings. Particularly is one apt to think of a cerebral accident if the patient is admitted in confusion or coma, without a history of antecedent pain. The peripheral neurological signs may also focus the attention on the cerebrum or spinal cord.

Pulmonary.—The pulmonary signs may be marked. A number of cases have been diagnosed as pneumonia and given chemotherapy or antibiotics. In some patients, thoracentesis was done for suspected cardiac or tuberculous effusion. Left hemothorax should always lead to the suspicion of dissecting aneurysm. At necropsy, blood was found in one or the other pleural cavity in nine of our cases.

TABLE III. PRIMARY AND SECONDARY ANTE-MORTEM DIAGNOSES

PRIMARY		SECONDARY	
Cerebral accident	9		
Hypertensive heart disease	10	Hypertensive heart disease	4
Acute myocardial infarction	4	Coronary occlusion	4
Arteriosclerotic heart disease	2	Arteriosclerosis	3
Cardiac failure	3		
Dissecting aneurysm	9	Dissecting aneurysm	2
Embolism to femoral artery	1		
Bleeding ulcer	1	Bleeding duodenal ulcer	1
Uremia	2		
Pneumonia	1	Pneumonia	3
Carcinoma of esophagus	1		
Echinococcus cyst of liver	1		

Abdominal.—Symptoms referable to the gastrointestinal tract may occasionally be prominent. In 60 per cent of our cases in which pain was a symptom, the onset was with pain in the epigastrium. If the dissection has involved some of the gastric or mesenteric vessels, hematemesis or melena may lead one to suspect an intrinsic gastrointestinal lesion. Finklestein and Jacobi[41] have emphasized that the only symptom in dissecting aneurysm may be abdominal pain simulating peptic ulcer. In a number of our cases, tentative diagnoses of bleeding ulcer or carcinoma of the esophagus or stomach had been considered. The presence of an abdominal mass may further obscure the picture. Reich[6] found that 21 per cent of his cases had an abdominal tumor, and in one-half of these a diagnosis of abdominal malignancy was made.

Renal.—The last and least frequent syndrome is that in which renal symptoms are prominent. Rogers[19] and Buckley[42] have reported cases in which hematuria and back pain have been the outstanding symptoms. If this clinical picture is present, attention may then be directed toward the renal areas rather than the aorta.

CONCLUSIONS

1. The clinical and pathologic features of dissecting aneurysm are discussed.

2. Of the forty-four cases in the series we are reporting, eleven were diagnosed ante-mortem.

3. Sixty-seven per cent of the cases were in men, with the great majority occurring in the fifth and sixth decades.

4. Pain in the abdomen or chest is usually a prominent symptom, but no history of this was obtained in 55 per cent of our cases.

5. The sequence of events in the progress and radiation of the pain may be of diagnostic importance.

6. Dyspnea and neurological disturbances are other important symptoms.

7. The various physical findings are discussed. Emphasis is placed upon the diagnostic value of hemothorax, of the diastolic murmur of aortic regurgitation, and of the bizarre neurological findings.

8. The varied features presented by dissecting aneurysm of the aorta allow us to divide these cases into five syndromes; cardiovascular, pulmonary, cerebral, gastrointestinal, or renal.

9. An awareness of these syndromes, and a realization that any individual case may fall into one or all of these groups, should increase the frequency with which dissecting aneurysm is accurately diagnosed prior to necropsy.

The authors are extremely indebted to the medical chiefs and referring physicians of Philadelphia General Hospital and Jewish Hospital for permission to include their cases in this study.

ADDENDUM

The following are brief summaries of eleven of our fourty-four cases which were diagnosed clinically.

CASE 4.—M. R., a physician 60 years of age, was admitted to the service of Dr. Mitchell Bernstein at Jewish Hospital on July 5, 1938, in a state of coma. The only history obtainable was the sudden development of unconsciousness. Examination revealed a temperature of 99° F., a pulse rate of 110, respirations of 40 per minute, and a blood pressure of 190/110. There was an obvious right hemiplegia and a systolic apical bruit. Death occurred in a few hours. Though the most likely diagnosis was that of hypertensive disease with a left cerebral thrombosis, the diagnosis of dissecting aneurysm was also made. This was confirmed at necropsy.

Diagnosis in this case depended upon a high degree of clinical suspicion. The suggestive findings were the sudden collapse, coma, and right hemiplegia. The average case with such a paucity of findings will probably escape recognition.

CASE 6.—D. M., 74 years of age, was admitted to the medical service of Dr. Harold Goldburgh, Jewish Hospital, on April 13, 1939. The patient had had mild effort angina and syncope for ten years. Two days prior to admission he experienced sudden severe bilateral lumbar pain. This was promptly followed by collapse. When admitted, the patient was pale and restless: the temperature was 101.3° F., the pulse rate, 120; respirations, 25 per minute; and blood pressure 90/60. There was a palpable mass in the left inguinal region, and a large ecchymosis over the left lumbar area. Leucocytosis, severe anemia, and elevation of the blood urea nitrogen were present. A number of red blood cells were found in the urine. The picture (proven at necropsy) seemed typical of ruptured dissecting aneurysm of the abdominal aorta.

Many of the classic signs are presented in this case. The severe lumbar pain followed by collapse, the elevated temperature, pulse, and respirations, the abdominal mass, the large left lumbar ecchymosis, and the hematuria were all typical of dissecting aneurysm.

CASE 8.—J. D., 58 years of age, was readmitted to the medical service of Dr. Harold Goldburgh at Jewish Hospital on November 26, 1940. He had been seen in the cardiac clinic for four years, and had experienced a severe myocardial infarction in 1939. While attending the cardiac clinic on the day of admission, he was seized with severe pain in the epigastrium. He broke into a profuse sweat and became dyspneic. On admission, the patient was obviously quite ill. Cyanosis, hypertension, cardiac enlargement, and cardiac failure were found. The femoral pulses were obviously unequal. Fever, tachycardia, tachypnea, and anemia developed. In view of his previous myocardial infarction, the diagnosis of acute myocardial infarction seemed likely. However, enough variations from the expected picture of myocardial infarction were present to support a tentative diagnosis of dissecting aneurysm. Death occurred four days after admission. At necropy, inactive mitral rheumatic involvement was found, and a number of healed infarcts in the left ventricle. Death was due to a dissecting aneurysm which began in the abdominal aorta and involved both iliac arteries.

At first glance this was considered an acute myocardial infarction. However, the epigastric pain, the unequal femoral pulses, and the progressive anemia suggested an acute dissecting aneurysm.

CASE 9.—B. K., a 65-year-old physician, was admitted to the medical service of Dr. A. Margolies at Jewish Hospital on May 19, 1941. He had been a known hypertensive for a number of years and had previously recovered from a posterior myocardial infarction. In the summer of 1940, while on vacation, he experienced an attack of chest pain that was considered to be due to acute myocardial infarction, though the electrocardiograms did not confirm this diagnosis. When he returned to Philadelphia, orthodiagraphy revealed progressive increase in the size of the aorta. Hematemesis occurred, and a gastroenterologist who saw the patient felt that cirrhosis of the liver with esophageal varices was present. Dyspnea and cough increased, the hematemesis became more marked, and the aortic dilatation increased. Following a profuse hemorrhage, he was admitted to the hospital with a diagnosis of aneurysm of the aorta, with dissection and erosion into the esophagus. Death occurred in two days. Autopsy revealed a large dissecting aneurysm of the arch that had eroded into the esophagus, and two small saccular aneurysms of the thoracic aorta.

This case was diagnosed nine months before death. The progressive dilatation of the aorta following an episode of chest pain was demonstrated by orthodiagraphy. The erosion into the esophagus, cough, and hematemesis were valuable contributory findings.

CASE 15.—S. L., 53 years of age, was admitted to the medical wards of Philadelphia General Hospital on December 7, 1936. She had had two or three previous hemiplegias. The day prior to admission she experienced severe pain in the abdomen and back and, when admitted, was confused and semistuporous. Because of the confusion, the severe hypertension, the increase in temperature, pulse, and respiration, the elevated blood urea nitrogen, and the presence of red blood cells in the urine, a tentative diagnosis of dissecting aneurysm was made and confirmed at necropsy five days later.

The picture was fairly characteristic. The severe pain in the back and abdomen, mental confusion, increased temperature, pulse, and respiration rates, and hematuria were the diagnostic guide posts.

CASE 16.—J. H., 58 years of age, was admitted to Philadelphia General Hospital, service of Dr. Kalteyer, on June 23, 1937. Two days prior to admission he had experienced sudden severe epigastric pain that apparently did not respond to narcotics. It began to travel down the left side to the back and lower ribs. Dyspnea developed and became severe. On admission, the temperature was 100° F.; pulse rate, 120; respiration, 25 per minute; and the blood pressure, 132/98. Auricular fibrillation and a mitral systolic murmur were found. A pericardial friction rub was present, and the electrocardiogram was reported as diagnostic of pericarditis. Upon thoracentesis,

blood was obtained from the pleural and pericardial cavities. A diagnosis of dissecting aneurysm of the aorta with rupture into the pericardium was made by Dr. S. Bellet. The patient lived for five weeks; necropsy confirmed the clinical diagnosis.

The diagnosis here depended on severe migratory epigastric pain that did not respond to narcotics, a pericardial friction rub with an electrocardiogram diagnostic of pericarditis, and the aspiration of blood from the pleural and pericardial cavities.

CASE 19.—S. L., 46 years of age, was admitted to the service of Dr. H. Jump at Philadelphia General Hospital on May 12, 1940. He had had severe hypertension for many years. On the day of admission, he developed severe abdominal pain and vomiting. Dyspnea was also present. On admission, the temperature was 100° F.; pulse rate, 120; respiration, 25 per minute; and blood pressure, 270/130. The left leg was definitely cooler than the right. A leucocytosis of 13,000 increased to 53,000 in twenty-four hours. A diagnosis of dissecting aneurysm was made. At necropsy, the dissection was found to extend from the arch of the aorta down to the bifurcation, involving both renal arteries and partially obstructing the left iliac artery.

In this patient, the suggestive findings were the severe abdominal pain associated with dyspnea, the immediate increase in temperature, pulse, and respiration rates, the several leucocytosis, and the marked decrease in the temperature of the left leg as compared to the right.

CASE 20.—H. F., 45 years of age, was admitted to the neurological service of Dr. A. Ornsteen at Philadelphia General Hospital on July 8, 1940. On admission, the patient was confused and no adequate history could be obtained. Hypertension was present, and there was paralysis of the left leg and paresis of the left arm. A diagnosis of cerebral malacia due to dissecting aneurysm was made and confirmed at necropsy ten days after admission.

The diagnosis of dissecting aneurysm was made in this case because of the confusion and the atypical neurological findings.

CASE 21.—D. M., 52 years of age, was admitted to the medical service of Dr. D. Kramer, Philadelphia General Hospital, on May 17, 1940. On the day of admission he had suddenly become dizzy, experienced a choking sensation, and collapsed. He was semiconscious upon admission. Temperature, pulse, respiration, and blood pressure were all normal. The electrocardiogram suggested a possible posterior myocardial infarction. Because of the history and the presence of systolic and diastolic murmurs at the aortic area, a diagnosis of dissecting aneurysm of the aorta was considered. Death occurred in two days. The diagnosis was confirmed at necropsy.

Collapse and semiconsciousness together with the presence of systolic and diastolic murmurs at the aortic area were the basis for the diagnosis.

CASE 30.—M. D., 50 years of age, was admitted to Dr. D. Kramer's medical service at Philadelphia General Hospital on November 8, 1941. She had had hypertension for a number of years. For two weeks prior to admission she had complained of pain in the substernal area, cough, and dyspnea. The pain radiated to the shoulder blades. On admission, the temperature was 100° F.; pulse rate, 130; respirations 45 per minute; and blood pressure 300/180. There was flatness in the left chest; repeated thoracentesis always yielded bloody fluid. A systolic aortic murmur was heard, the murmur apparently continuously changing in character. Gradually the pain shifted from the interscapular area to the left chest and abdomen. None of the repeated electrocardiograms were diagnostic of myocardial infarction. The patient lived for two months, and at necropsy, the diagnosis of dissecting aneurysm with rupture into the pericardium and left pleural cavity was confirmed.

The important findings in this patient were the migrating chest and interscapular pain, the changing systolic murmur, and the recurrent left hemothorax.

CASE 40.—F. S., 57 years of age, was admitted to the medical service of Dr. S. Loewenberg, Philadelphia General Hospital, on November 7, 1945. His history prior to admission was interesting. He had had hypertension for years. Six months previous to admission there developed a gradual paresis of the left leg. This improved, but two months later he suddenly collapsed. His legs were unable to bear his weight. After a few days, their strength partially returned, but a cane was needed for support. On the day of admission, he suddenly collapsed, lost the use of

both legs, and complained of dyspnea. The temperature was 100° F.; pulse rate, 110 per minute; respirations, 36; and blood pressure, 270/130. The heart was enlarged and mild cardiac failure was present. The patient seemed to be slowly regaining the use of his legs, but death from respiratory failure occurred suddenly three days after admission. A diagnosis was made of thrombosis of the anterior spinal artery, possibly due to dissecting aneurysm. At necropsy, the dissection was found to extend to the renal artery on the left, with some involvement of the anterior spinal artery at that level.

The importance of the bizarre neurological changes as a basis for the diagnosis of dissecting aneurysm are well exemplified in this case.

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CHANGES IN THE CORONARY ARTERIES OF THE DOG FOLLOWING INJECTIONS OF ALLYLAMINE

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NECROSIS of the walls of arteries may occur as a part of general necrosis of tissue. It occurs more selectively in typhoid fever, typhus, tuberculosis, rheumatic fever, periarteritis nodosa, lupus erythematosus, serum sickness, and other conditions. Necrotizing arteritis is a prominent feature of malignant nephrosclerosis. The basic morphologic change in the arterial wall is fibrinoid necrosis of the media accompanied by more or less cellular exudate involving the vessel wall and often the periadventitial tissues. This exudate may vary in the type of constituent cell. Thrombi may complicate the picture.

Changes of a similar character have been produced in the experimental animal by several procedures. These include, among others, renal ischemia in dogs,[1,2] sensitization of rabbits by the injection of horse serum,[3] and unilateral nephrectomy in rats combined with injections of desoxycorticosterone.[4] Subcutaneous injections of trypsin,[5] besides digesting tissues locally, has led to segmental necrosis of artery walls.

The necrotizing vascular lesions which follow bilateral renal artery ligation in the dog seem to be associated in part with the presence within the body of ischemic kidney tissue.[6] With this fact in mind, the literature was searched to see if any derivative of tissue breakdown was known to result in such lesions when injected into animals. The report of Mellon and associates[7] was of particular interest. These investigators reported the production of acute arterial lesions locally in rabbits that had been injected intradermally with low concentrations of a buffered unsaturated aliphatic amine, allylamine: $CH_2 = CH - CH_2 - NH_2$.

Mellon and associates had become interested in this substance through the work of Eppinger and co-workers.[8] Eppinger had identified allylamine as a toxic substance in the tissues of animals dying of experimental paratyphoid infections, and had shown that pure solutions injected intravenously caused great increase in capillary permeability and marked edema of blood vessel walls,

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of the heart valves, and of the gastric and duodenal mucosa. These observations seemed to warrant further investigation.

The work herein reported presents the results of injections of allylamine and of related substances intravenously in dogs together with the results of a few intrapericardial injections of the same materials.

METHODS

Allylamine is a strong base. For injection it was prepared as a 1 per cent aqueous solution neutralized with hydrochloric acid and buffered to pH 7.4. Fifteen milligrams per kilogram of body weight of the base were injected initially. At this level, severe immediate reactions were avoided. N-propyl amine, used as a control for the allylamine, was prepared in the same way and was injected in the same doses. Allyl alcohol and other nonbasic homologs were injected as 1 per cent aqueous solutions at pH 7.4, at the same dosage levels.

The intrapericardial injections were made under direct vision through a chest incision, utilizing nembutal anesthesia and positive pressure respiration. Ten cubic centimeters of the sterile buffered solution was placed in the pericardial sac through a small needle.

Following an intravenous injection of 15 mg. per kilogram of allylamine, there is no immediate reaction. Within a few minutes the dog usually becomes restless and may vomit and defecate. These signs continue for some minutes, then disappear. The majority of dogs survive 20 mg. per kilogram as an initial dose, but may become wildly excited for fifteen or twenty minutes. With this dose some die within twelve to twenty-four hours. With higher doses severe reactions are common and within a few hours the animals become prostrated with a falling blood pressure and a remarkably increased hematocrit. Death occurs in stupor. In dogs, even lethal doses have no immediate effect on the systemic blood pressure. In rabbits, very large doses of the amine injected intravenously lead to marked pupillary constriction after some minutes.

The majority of dogs in the present experiment were given two or more doses of the amine, as it was found that the changes occurring in the cardiovascular system increased and became progressive with repeated injections. The usual procedure was to give an initial dose of 15 mg. per kilogram and to follow it with a similar dose twenty-four to forty-eight hours later. Further injections might be given at intervals of two or three days, depending on the condition of the animal and the purpose of the experiment. It was found after the first few injections that most dogs would tolerate injections of 20 mg. per kilogram every three to five days. In the chronic experiments the animals were watched carefully and were rested, if necessary, at any stage before continuing injections. In spite of these precautions unexpected deaths in the series have occurred.

Although some acute changes in the cardiovascular system were observed in animals dying in the first twenty-four hours following a single injection of allylamine, these changes were best seen in animals three or four days after the last of two or three injections given as indicated. More chronic, progressive

changes, as well as acute lesions, have been found in animals surviving longer periods and given repeated doses.

In all, the tissues of about fifty dogs have been examined. The formalin fixed sections have been stained with Masson's trichrome method, hematoxylin and eosin, Weigert's elastic tissue stain, and Sudan IV.

RESULTS

The changes following intravenous injections of allylamine involve particularly the medium-sized and smaller muscular coronary arteries, the arteries of the retroperitoneal mesenteric fat, the peripheral body fat itself, and, to a lesser extent, the myocardium, the kidneys, and the liver.

Changes Following a Single Lethal Dose.—In animals dying six to twenty-four hours after a lethal dose, there is little to be seen grossly or microscopically except for large zones of extravasated fluid in the retroperitoneal and epicardial fat. Occasionally, massive hemorrhages may be found in these regions as well. While the majority of the blood vessels at this interval are not strikingly altered, a few in the epicardial fat have clear, swollen medial cells, and an occasional epicardial vessel with a fused, fuchsinophilic, edematous media has been observed. Accompanying cellular exudate has been present. There may be cloudy swelling and interstitial edema of the liver and kidneys. These changes have been noted at this interval only after large, rapidly fatal, intravenous injections.

Acute Changes Following Repeated Intravenous Injections.—Survival for three to four days after two or three injections of allylamine, 15 mg. per kilogram, is associated with striking changes in the blood vessels and adipose tissue. Grossly, there are petechial and confluent hemorrhages in the epicardial fat. The fat itself is indurated and discolored. Similar changes are present in the mesentery.

Microscopically, the medium-sized and smaller muscular coronary arteries, both superficial and penetrating branches, are the seat of an intense acute necrotizing process (Figs. 1 and 3). Many vessels are involved, the changes varying in stage and intensity. Segments of the medial smooth muscle are fused into amorphous, brightly acidophilic masses. Numbers of extravasated red blood cells may be present in the media or adventitia, or both. Polymorphonuclear leucocytes and large mononuclear cells may be present in the necrotic media and in the surrounding adventitia, but they may be few in number or be entirely absent. The perivascular exudate may be composed solely of mononuclear cells. No esosinophilic leucocytes have been encountered in the lesions studied. While the internal elastic membrane usually remains intact, it may be thin, swollen, or frayed. There is very little other elastic tissue in vessels of this size in the dog's heart. In vessels in which the medial changes are more advanced, no remnant of the smooth muscle fibers can be identified. The medial segment appears shrunken and is composed of a homogeneous ground substance that takes a light green stain with Masson's method.

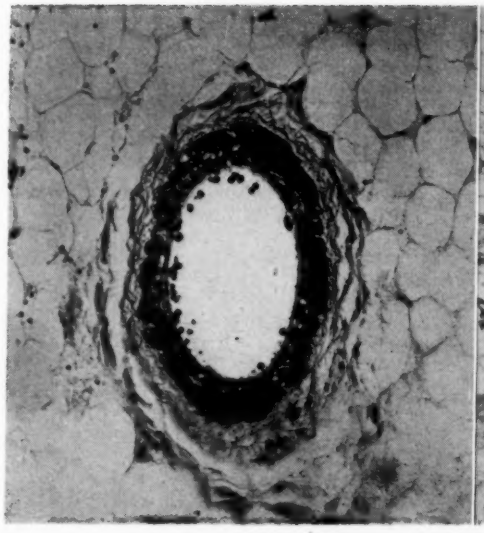

Fig. 1.

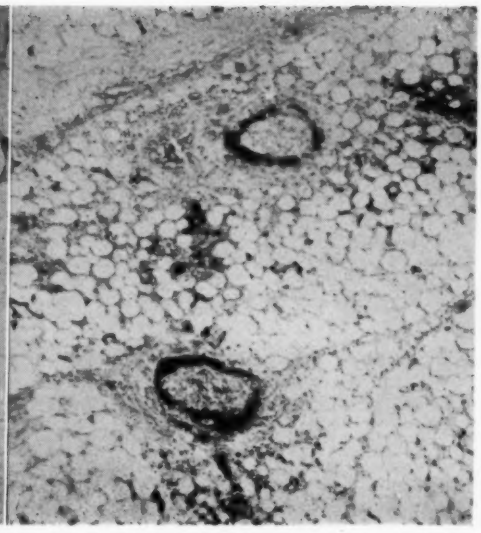

Fig. 2.

Fig. 1.—Dog. Coronary artery four days after two intravenous injections of allylamine. Fibrinoid necrosis of media. Lack of periadventitial and advential inflammation. x 165.

Fig. 2.—Dog. Arterioles in mesenteric fat four days after three intravenous injections of allylamine. Acute necrotizing arteritis. Perivascular cellular exudate. Hemorrhage and exudate in fat. x 75.

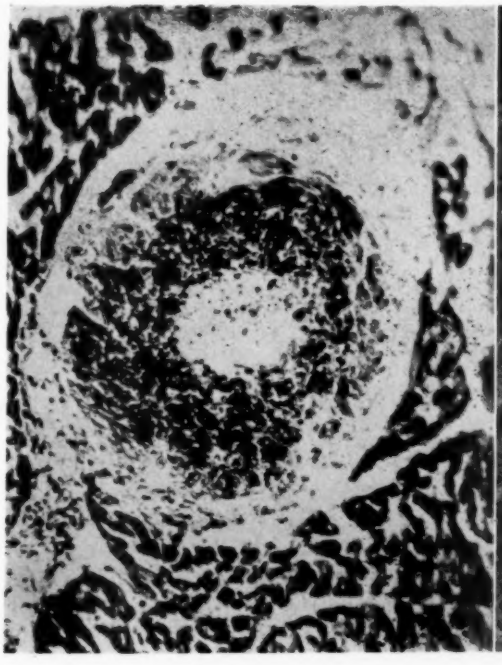

Fig. 3.

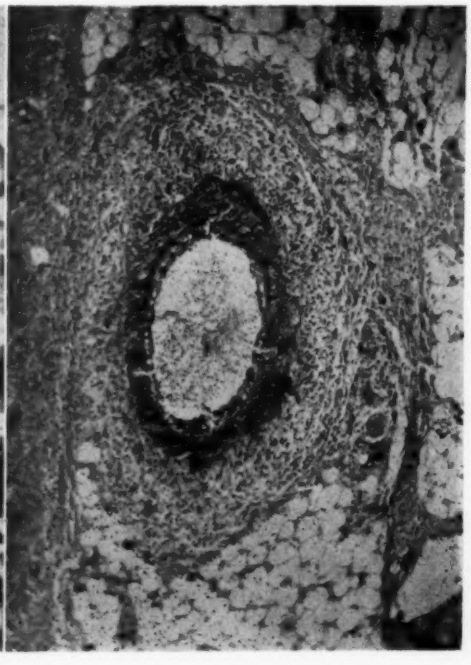

Fig. 4.

Fig. 3.—Dog. Coronary artery, penetrating branch, of left ventricle four days after two intravenous injections of allylamine. Periadventitial cellular exudate. Fibrinoid necrosis of and hemorrhage in media. x 80.

Fig. 4.—Dog. Coronary artery four days after two intravenous injections of allylamine. Periarteritis. Small area of fibrinoid necrosis of media. Elevation of endothelium. x 120.

The intima of the muscular coronary arteries of the dog consists of the endothelium lying directly on the internal elastic membrane. In severely damaged vessels, a segment or the whole circumference of this endothelium is raised from the underlying elastic membrane and fluid and mononuclear cells appear in the thus created subendothelial space (Figs. 4 and 5). Thrombi have only occasionally been observed in the lumina of the involved coronary vessels. The detached endothelium with its underlying fluid and cells may extend far into the lumen of the vessel.

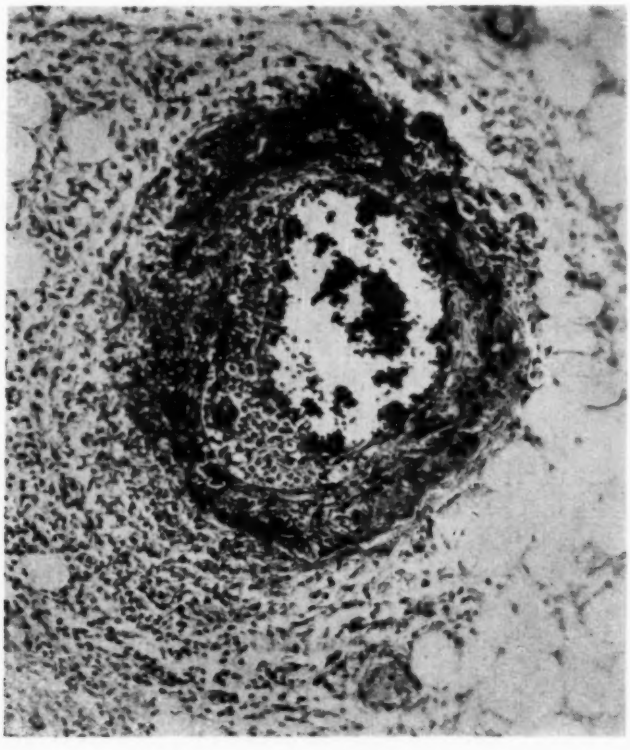

Fig. 5.—Dog. Coronary artery five days after three intravenous injections of allylamine. Intense periarterial exudate. Fibrinoid necrosis of media. Elevation of endothelium. Subendothelial space filled by a mosaic of large clear mononuclear cells. Erythrocytes in reduced lumen. x 200.

Hemorrhage into the vessel walls, even in the smallest arteries, is prominent and appears to arise from the vasa vasorum in the adventitia and outer media. The red blood cells may be found throughout the media and even in the subendothelial space formed by the elevation of the endothelium.

Acute alterations in the mesenteric arterioles and in fat elsewhere in the retroperitoneal region are similar to those in the coronary arterioles, although the number of vessels involved is usually less (Fig. 2). No vascular changes of a similar nature have been seen after allylamine injections in the kidneys, liver, gastrointestinal tract, or other viscera.

Extravasated fluid in the depot fat has been described as an early finding after large single injections of allylamine. This exudate is seen in animals also after smaller repeated doses devised to allow longer survival. In these dogs there is precipitation of a fibrillar substance, probably fibrin, in the fluid as well, and there may be focal or diffuse cellular reaction. Necrosis of fat is not prominent, but probably occurs. Focal hemorrhages are numerous. Vessel changes in the epicardial fat seem to develop simultaneously with those in the fat itself. Very early many of the capillaries appear to contain hyaline thrombi, but it is difficult to ascertain whether or not the changed appearance of these vessels is due to a luminal mass or to an altered condition of the wall.

Cloudy swelling and interstitial edema may be present in the kidney and liver. There may be, in some animals, fatty change in the renal tubules. In no instance has this led to nitrogen retention. Small, focal myocardial necroses are present in many animals. Occasionally, these are extensive.

Changes in Animals Repeatedly Injected and Allowed to Survive Six Weeks or Longer.—In animals repeatedly injected and allowed to survive a longer period of time, a progression of the changes already described occurs. Additional coronary vessels of the same caliber are involved in the acute necrotizing process. The medial coats of those involved early are now composed entirely of fibrous connective tissue. Fresh hemorrhages may be present, however, in the altered media. In many vessels striking changes have occurred in the intima. The undifferentiated mononuclear cells that accumulate beneath the endothelium are transformed into masses of connective tissue with newly formed blood vessels.

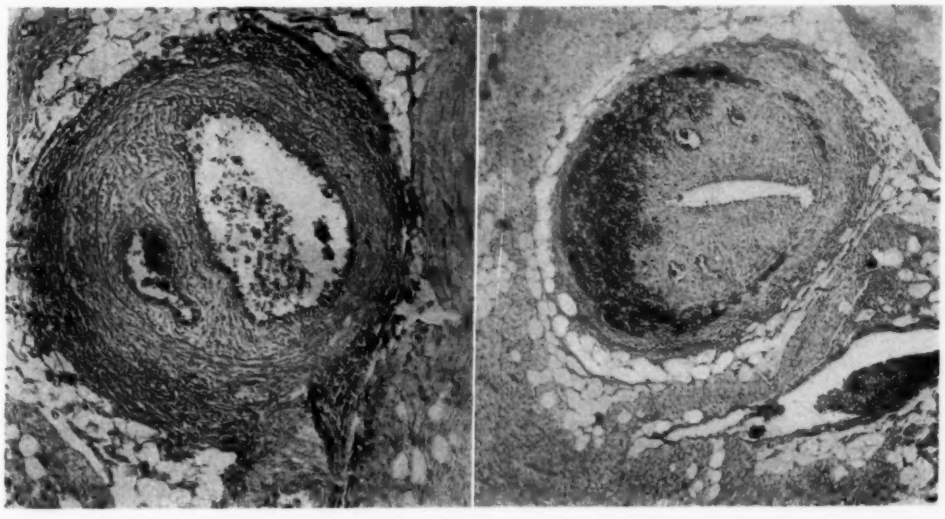

Fig. 6. Fig. 7.

Fig. 6.—Dog. Coronary artery after six weeks of a course of twelve intravenous injections of allylamine. No acute inflammatory changes. Fibrosis of media. Fibrous proliferation of intima with reduction of lumen and a new vascular channel. Note the internal elastic membrane. x 320.

Fig. 7.—Dog. Coronary artery after six weeks of a course of fifteen intravenous injections of allylamine. Thin fibrous media. Massive intimal proliferation with new blood vessel formation. Hemorrhage in media and intima. Original lumen of vessel reduced to a central slit. x 140.

This granulomatous endarteritic process may seriously encroach on the lumina of the vessels. Thrombi are usually not present. There may be massive hemorrhages into the thickened, intimal tissue. Fat stains of such vessels so far have revealed lipoidal substances only in areas of hemorrhage. Twelve to fifteen injections over a period of six weeks resulted in the changes described (Figs. 6 and 7). Lesions were not equally developed in every animal. There is a large individual variation.

Chronic changes in the body fat consist in a progressive fibrosis with some giant cell reaction. Hemorrhagic areas become organized. A few arterioles may be found with greatly thickened fibrous walls, and reduced lumina.

Fatty livers have been observed regularly in dogs kept on allylamine injections for six weeks or longer. In this connection it should be mentioned that unless rest periods are given, the dogs eat very little and lose weight rapidly. If the drug is discontinued, they resume eating and appear normal.

Changes Following Intrapericardial Injections of Allylamine.—In order to see if the coronary arteries would be injured locally by allylamine, 10 c.c. of the neutralized 1 per cent solution was injected directly into the pericardial sacs of a series of normal dogs (Figs. 8, 9, and 10). After twenty-four hours, there were gross hemorrhages and induration of the epicardial fat. Dogs examined after four days revealed the most extensive necrotizing and endarteritic changes in the muscular coronary arteries. These changes are qualitatively like those following intravenous injection. Invariably, however, the segment of the vessel nearest the epicardial surface was most intensely involved. The fibrinoid change tended to occur first in the outer layers of the media, and there was much more periarterial cellular exudate.

The arterioles of the parietal pericardium are also involved. There is a mild fibrinous pericarditis, with changes in the subepicardial fat similar to those occurring after intravenous injection. No lesions were found elsewhere in the body. The more chronic changes occurring in the coronary vessels following repeated intrapericardial injections of allylamine are being investigated.

Changes Following Bilateral Nephrectomy and Injections of Allylamine.—Acute necrotizing arteritis of the coronary arteries and of the arterioles of the mesenteric fat were found in three bilaterally nephrectomized dogs injected with allylamine.

Control Groups.—Control groups of dogs have been given intravenous injections of n-propyl amine, allyl alcohol, allyl formate, allyl thiourea, and allyl chloride according to the same dosage plan and in equal gram-per-kilogram doses. N-propyl amine and allyl alcohol have been injected intrapericardially. The animals have been studied three to four days after the last injection. Comparable vascular lesions have not been found. One necrotic arteriole in the liver of a dog receiving allyl formate intravenously was observed. This liver was the seat of widespread parenchymatous necrosis. Edema of the submucosal gastric vessels, but no necrosis, was observed after intravenous injections of allyl alcohol. These vascular changes formed part of the massive hemorrhagic edema of the stomach

Fig. 8.

Fig. 8.—Dog. Inner portion of wall of large coronary artery five days after one injection of allylamine intrapericardially. Edema and fibrinoid necrosis of medial cells. Cellular exudate in necrotic media. Elevation of endothelium with masses of small mononuclear cells in the subendothelial space (these are not red blood cells). x 45.

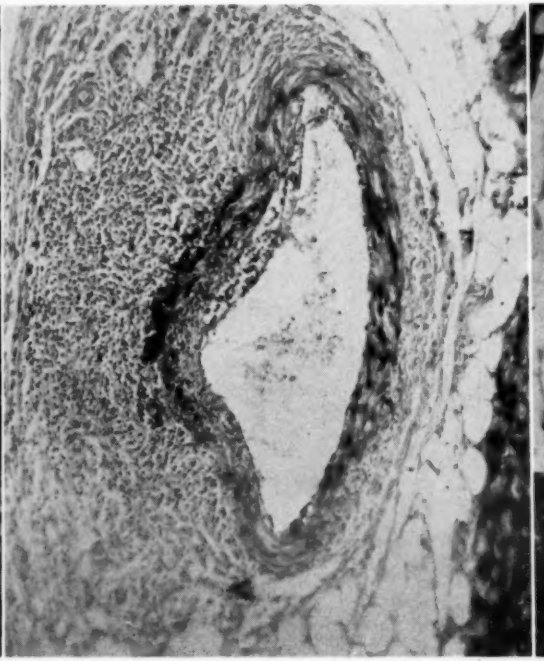

Fig. 9.

Fig. 9.—Dog. Coronary artery five days after one injection of allylamine intrapericardially. Segmental perivascular inflammatory reaction. Advanced medial necrosis. Elevation of endothelium with subendothelial mononuclear exudate.

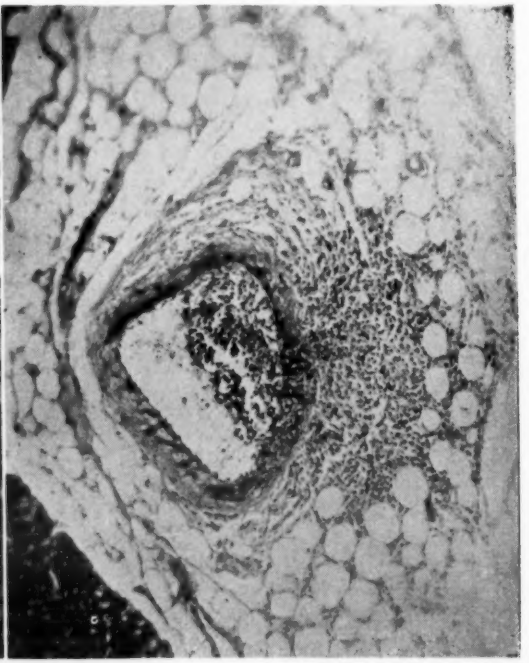

Fig. 10.

Fig. 10.—Dog. Another coronary artery from same animal as Fig. 9. Sharp segmental localization of mural changes. Subendothelial exudate. Lumen reduced nearly one-half.

that was regularly observed following intravenous injections of allyl alcohol. This lesion, first described by Eppinger, will be the subject of a subsequent report.

Injections of allylamine into a few rabbits and rats has led to the preliminary conclusion that these species do not regularly develop, at these dose levels, the vascular lesions described. Changes in the body fat similar to those in the dog have been observed.

DISCUSSION

Injection of allylamine in dogs affords a relatively simple, concrete starting point for a study of the pathogenesis and fate of arterial lesions that are basically like those occurring in certain diseases of man. Time and further experimentation will be required to evaluate the effect of the progressive changes in the coronary arteries on the total physiology of the heart. Much further experimentation, some of which is now in progress, will be needed to ascertain what role, if any, volatile unsaturated amines or related substances play in the etiology and pathogenesis of diseases in man or in the experimental animal. Finally, in allylamine, a tool is provided for the investigation of the relationship, if any, of acute vascular disease to the more common chronic forms of disease of the arterial wall.

SUMMARY

Preliminary report of the pathologic changes occurring in dogs after single and repeated injections of allylamine and related substances has been made. The progressive morphologic changes occurring in the coronary arteries and in the body fat have been described in some detail. The similarity of the vascular lesions to those occurring in certain diseases of man has been pointed out and plans for further study indicated.

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THE EFFECT OF LOCAL COMPRESSION UPON BLOOD FLOW IN THE EXTREMITIES OF MAN

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THE question as to whether the circulation in the limbs is significantly reduced by the application of moderate local pressure is of interest not only to specialists in peripheral vascular disease, but also to surgeons, orthopedists, and others concerned with the application of constricting apparatus on the limbs. This is because of the recent recognition of the fact that warmth and health of the extremities depend directly upon the adequacy of their circulation, and only indirectly upon the abundance of insulation around them. A great deal of attention, therefore, has been paid by the Armed Services, for example, to the circulatory effects of constricting clothes, gloves, and shoes,[1] especially in cold environments where they have been found to be of importance in the incidence of frostbite and of immersion or trench foot.

Previous studies in this laboratory[2] have demonstrated a reduction in blood flow to the extremities during elevations of venous pressure produced by inflating pneumatic cuffs on the proximal portion of the limbs. The present study was undertaken to determine the effects of mild to moderate external compression, uniformly applied to different parts of normal extremities, upon the local blood flow. Three methods previously found valid for estimating blood flow in the extremities under such conditions were used: (1) thermometric, (2) blood gasometric, and (3) plethysmographic.

METHODS AND RESULTS

Thermometric Method.—The temperature of the skin provides an index of circulatory changes in the skin when the environmental temperature is maintained at a relatively constant level, lower than body temperature. Such measurements are simple and easy to make, but have the disadvantages of being difficult to quantitate in terms of volume of blood flow, and of having too much lag to allow the detection of fleeting circulatory changes.

In the present experiments, copper-constantan thermocouples were attached to at least two corresponding finger pads of each hand. The hands were

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sealed in airtight plethysmographs,[3] out of which the thermocouple wires were led to a galvanometer through a selector switch. A centigrade mercury thermometer was inserted into each plethysmograph for the measurement of air temperature within the apparatus. Every three to five minutes, galvanometer readings were made, accurate to 0.1° C., measuring the temperatures of the several finger pads in rapid succession; the plethysmograph temperatures were also recorded.

The subjects lay in an air-conditioned room, and were comfortably warmed with blankets and heating pads so as to produce mild peripheral vasodilatation. After a control period of ten to twenty minutes the air pressure within one of the plethysmographs was increased to 20 or 30 mm. Hg above atmospheric by connecting it through a valve to a large bottle containing air at the desired pressure. The opposite plethysmograph was kept at atmospheric pressure for control observations. After ten to sixty minutes of pressure, the plethysmograph was deflated and another period was allowed for control conditions to be resumed. Then, either the same hand was exposed to a different pressure, or was utilized as the control while pressure was applied to the opposite hand.

The results of a typical experiment are illustrated in Fig. 1. The temperatures of the fourth finger of the right hand (RF_4) and of the corresponding finger of the left hand (LF_4) are graphed during the application and removal of the indicated pressures. In addition to the changes in skin temperature produced by local pressure, there occurred spontaneous variations due to vasomotor activity in the fingers which tended to be similar on the two sides. In order to lessen the confusion introduced by these spontaneous changes, the *difference* in temperature between the right and left fourth fingers is plotted at the bottom of the figure, with increasing positive values denoting an increase in the temperature of the right side relative to that of the left. The graph shows that when 20 mm. Hg pressure was applied to the right hand, no clear-cut effect was observed except for similar spontaneous fluctuations on both sides. The same pressure applied to the left hand caused the temperature on that side to drop perceptibly, thus producing a rise of the difference curve. The subsequent application of 30 mm. Hg pressure on each side, in turn, was followed by a rather large decrease in relative temperature of that respective side.

Similar tests were carried out on five subjects, all with normal peripheral circulation. Uniformly, when positive pressure on the hands produced any effect, it caused a decrease in skin temperature as compared with that of the opposite control limb. A summary of the data is presented in Fig. 2. In each test, the temperatures were averaged for the periods before, during, and after each application of pressure, beginning five minutes after each change. The resulting figures from all the tests were then averaged and plotted in the graph. These mean values show that a local pressure as small as 20 mm. Hg produced a definite reduction in skin temperature, while one of 30 mm. Hg resulted in a greater reduction, averaging about 1° centigrade. The mean decrease in skin temperature is shown in relation to local pressure in Fig. 3.

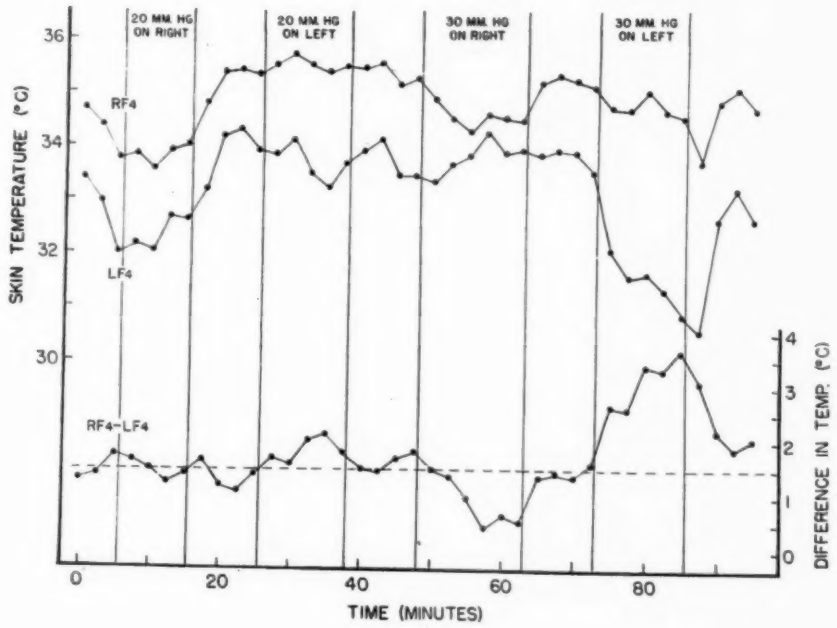

Fig. 1.—Typical experiment on the effects of local pressures of 20 and 30 mm. Hg on the skin temperature of the tips of the fourth finger of the right hand (RF_4) and left hand (LF_4). The lowest curve, showing the difference in temperature between RF_4 and LF_4, is presented in order to lessen the confusion introduced by spontaneous vasomotor changes. The broken horizontal line denotes the mean value of the temperature difference in the absence of pressure.

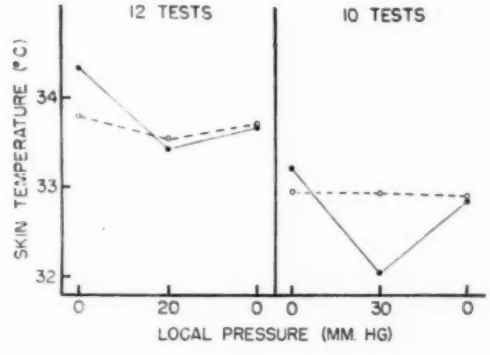

Fig. 2.

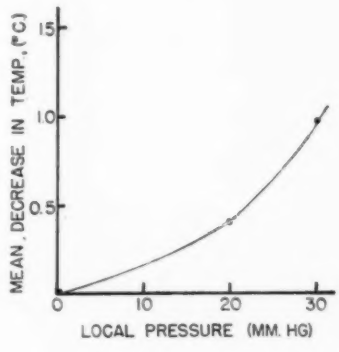

Fig. 3.

Fig. 2.—The mean effect of local pressure on the temperature of the fingertips. The average temperatures are indicated before, during, and after application of pressure. The solid lines represent the experimental hand, and the broken lines represent the opposite (control) hand.

Fig. 3.—The relation between local pressure and the mean decrease in the temperature of the fingertips in the experiments shown in Fig. 2.

Skin temperature measurements during the application of a pressure of 50 mm. Hg were carried out on two subjects. The mean decrease in finger tip temperature was 2.5° centigrade. During this time, moreover, the subjects were warmed so that the mean temperature of the control hand increased 2.3° centigrade. The effect of local compression of 50 mm. Hg, therefore, was a temperature reduction of 4.8° C. on the experimental as compared with the control side.

Blood Gasometric Method.—The blood flow through an organ may be determined, according to the Fick principle, by dividing its oxygen uptake by the arteriovenous oxygen difference. The rate of oxygen uptake by a given forearm under resting conditions has been shown to be fairly constant.[4] Likewise, the arterial oxygen content normally remains fairly constant. Changes in the blood flow through a resting forearm may therefore be estimated by determining the alterations in the venous oxygen content. If the blood flow decreases, more oxygen is extracted from a given volume of blood during its passage through the tissues and the venous oxygen content falls.

This method was applied to the present problem as follows. Blood was obtained from the antecubital veins of both arms before, during, and after compression of one forearm, the opposite arm serving as a control. In order to avoid repeated venipunctures, with concomitant reflex disturbances in circulation, indwelling needles with obturators (Unger type, gauge 18) were employed. Before each experiment these were inserted pointing distally into the veins through the skin, previously infiltrated with 1 per cent procaine hydrochloride. Blood samples could be taken, when desired, simply by removing the occluding stylets from the needles and attaching oiled syringes, containing sufficient heparin solution to fill the dead space in the tip. The blood samples were handled anaerobically and stored over mercury in a refrigerator. Each sample was analyzed in duplicate for content of oxygen by the technique of Van Slyke and Neill.[5] The allowable difference of duplicate analyses was 0.10 volume per cent. The arterial oxygen content was estimated from the oxygen capacity of the venous blood, assuming an arterial oxygen saturation of 96 per cent. Hematocrit determinations in duplicate were also made on each sample by the method of Wintrobe.[6]

Experiments were first done by a procedure (designated as *Method I*) which, as will be shown, proved to be unsatisfactory. Another group of experiments (designated as *Method II*) was performed by an improved technique. Finally, a series of *control* experiments was carried out in which no pressure was applied to either side.

Method I: These experiments were carried out according to the following procedure. The needles were inserted as described and pneumatic cuffs were applied snugly but without pressure, covering each forearm up to about 2 cm. below the tips of the needles. The hand circulation was occluded at the start of each experiment by inflating separate cuffs on the wrists at a pressure greater than systolic. After four to five minutes the first pair of blood samples was

taken. One forearm was then subjected to the desired pressure (20 or 30 mm. Hg) by inflating the cuffs. After four to five minutes a second pair of samples was obtained. The pressure on the forearm was then discontinued and a third pair of samples obtained after another four to five minute interval. Finally, the wrist cuffs were deflated.

The results of these earlier tests are summarized in Fig. 4. Graph *A* represents the mean of ten experiments in which a pressure of 20 mm. Hg was applied to one forearm (solid curve). During compression, the venous oxygen content decreased about 1 volume per cent. The mean arteriovenous oxygen difference thus rose from 6.4 to 7.4 volumes per cent, an increase of 15 per cent. The calculated blood flow correspondingly decreased 15 per cent. The averages for the opposite arm, which served as a control (broken curve) showed no significant change in venous oxygen content. With 30 mm. Hg pressure (Graph *B*), the mean decrease in venous oxygen content was somewhat greater, corresponding to a 20 per cent decline in calculated blood flow. The control arm showed a much smaller mean change, in the opposite direction.

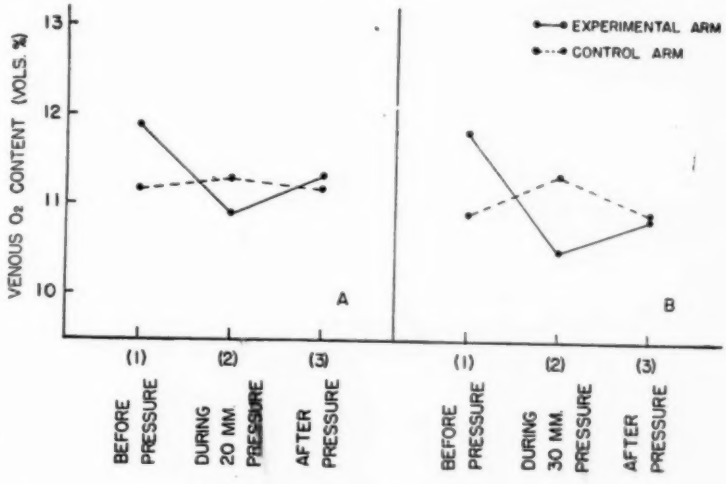

Fig. 4.—The mean results of the blood gasometric experiments performed by Method I. For reasons explained in the text, this method of sampling venous blood proved unsatisfactory during the application of pressure.

***A*, Mean oxygen content of venous blood from the arm during application and removal of 20 mm. Hg pressure. The average arterial oxygen content of this group of ten subjects was 18.3 vols. per cent.**

***B*, Similar data for experiments with 30 mm. Hg pressure. The average arterial oxygen content of this group of six subjects was 19.6 vols. per cent.**

A statistical analysis of the significance of the changes in oxygen content in these experiments was made by the method of Fisher.[7] It was found that the mean decrease in venous oxygen content on applying 20 mm. Hg pressure was barely significant ($P^* = 0.04$), while that on applying 30 mm. Hg pressure just

***P represents the probability that the observed change may occur by chance. Values of 0.05 or less indicate statistically "significant" changes, and those of 0.01 or less indicate "highly significant" changes.**

lacked statistical significance ($P = 0.06$). The recovery on releasing the pressure in both groups lacked significance (P values were 0.16 and 0.62, respectively). The spontaneous changes in the control arm were not significant (P values between 0.40 and 0.97). The relatively poor statistical significance of the experimental data obtained by Method I is attributable to the following observations.

Although local compression of the forearm caused a definite reduction in the oxygen content of the venous blood samples in most of the experiments with Method I, in others there was only a slight, or occasionally even a reversed, effect. Such aberrant results were obtained even when the venous blood flow, as judged by the ease of securing blood from the vein, was definitely decreased; in fact, the erratic results were most marked in just those instances when the blood was most difficult to obtain. This consideration caused doubt that the samples truly represented the venous blood issuing from the compressed area, but rather consisted of a mixture of such blood with that refluxing in the vein from above the compressed area. In order to obviate the possibility of such a mixing, the technique of sampling was changed in the subsequent experiments.

Method II: In the later tests, the Unger needles were inserted as before. However, a flexible venous catheter, stiff enough to withstand the compression of the cuffs, was attached to the needle on the arm to be compressed. The cuffs were applied and extended from the distal part of the forearm to the middle of the upper arm, covering the needle as well as the catheter leading upward from it. By sampling the venous blood from a site near the middle of the compressed area instead of at its proximal border, one might expect that the reflux of blood from noncompressed areas would be prevented. A constant slow drip of isotonic saline solution was instilled through the catheter and needle to keep them patent. At frequent intervals, measurements of venous pressure were made through this system by the technique of Moritz and von Tabora.[8] On the control side, the same sampling technique was used as in Method I. Samples were obtained by the same procedure as in the earlier experiments except that the initial 5 c.c. from the catheter were discarded to clear the system of saline solution.

The individual results of the experiments carried out with 30 mm. Hg pressure by the improved technique (Method II) are shown in Table I* and the mean results in Fig. 5 (left). The results obtained by this method *uniformly* showed that the venous oxygen content was decreased during compression. The mean arteriovenous oxygen difference rose from 6.8 to 9.1 volumes per cent, signifying a 25 per cent decrease in blood flow. On removal of the pressure, the oxygen content rose almost to its initial value. Statistically, these changes were highly significant, the P values being less than 0.01. The changes in the control arm were not significant, the P values when the pressure was applied and removed being 0.72 and 0.26, respectively.

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*The hematocrit values of samples obtained through the catheter often were not identical with those obtained from the opposite arm, probably due to slight dilution by the saline solution. However, the difference between the hematocrit determinations on corresponding samples rarely exceeded 0.5 per cent. In case of a difference, the oxygen content of the experimental sample was corrected by the factor necessary to equalize the hematocrits. The tables present the corrected oxygen contents.

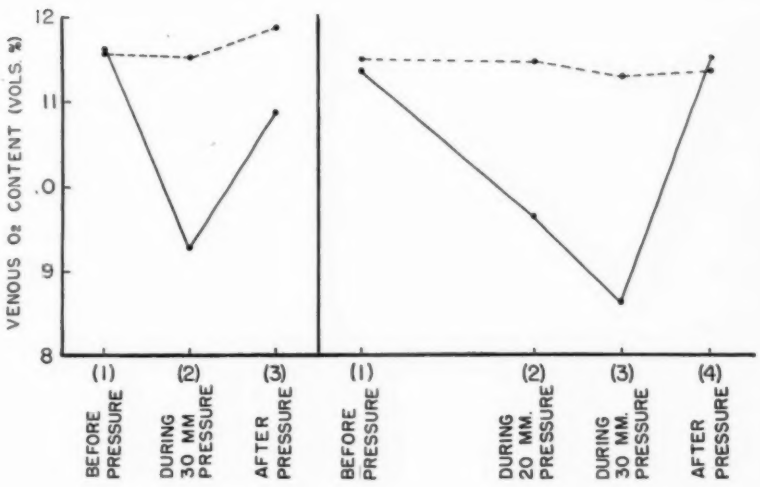

Fig. 5.—The results of the blood gasometric experiments performed by Method II. Each graph shows the mean data of five experiments (see Tables I and II for individual figures). The solid lines represent the arm on which the pressure was applied; the broken lines, the opposite control arm. The mean arterial oxygen contents of the two groups of subjects were 18.4 and 16.6 vols. per cent, respectively.

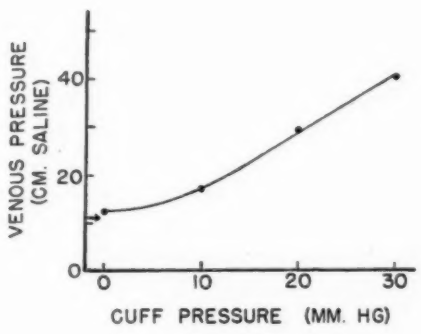

Fig. 6.

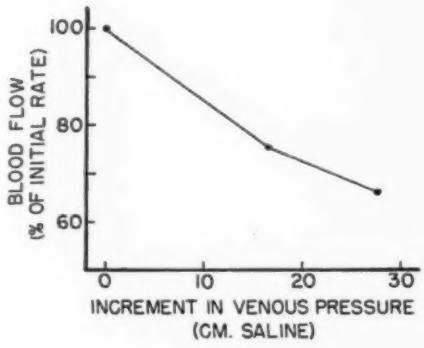

Fig. 7.

Fig. 6.—The relation between the pressure in the pneumatic cuffs on the forearm and the mean venous pressure beneath the cuffs. The venous pressures refer to the level of the needle in the vein as zero. The arrow represents the mean level of the sternum. Since 1 mm. Hg pressure is equivalent to about 1.34 cm. of saline, it is evident that the venous pressure becomes approximately equal to the cuff pressure.

Fig. 7.—The relation between the increment in venous pressure produced by the compressing cuffs and the relative blood flow, as determined by the blood oxygen method in the experiments reported in Table II.

TABLE I. THE VENOUS OXYGEN CONTENTS IN THE EXPERIMENTS WITH 30 MM. HG PRESSURE (METHOD II)

SUBJECT	VENOUS OXYGEN CONTENT (VOLS. PER CENT)						ESTIMATED ARTERIAL OXYGEN CONTENT (VOLS. PER CENT)
	EXPERIMENTAL ARM			CONTROL ARM			
	BEFORE PRESSURE 1	30 MM. PRESSURE 2	AFTER PRESSURE 3	1	2	3	
Gun.	12.87	10.51	12.30	13.30	13.05	12.48	18.5
Swe.	10.95	8.69	10.30	11.93	12.16	12.00	19.3
Ada.	9.52	7.87	9.66	9.14	8.50	9.25	16.8
Cro.	13.84	10.39	11.65	12.85	11.40	12.98	18.8
Atw.	10.93	8.96	10.45	10.62	12.45	12.51	18.7
Mean oxygen content	11.62	9.28	10.87	11.57	11.51	11.84	18.4
Standard deviation	1.72	1.14	1.03	1.70	1.78	1.49	1.0
Mean A-V difference	6.8	9.1	7.5	6.8	6.9	6.6	
Mean hematocrit (per cent)	41.1	42.2	42.1	43.0	43.3	42.4	

Additional experiments with Method II were carried out on five subjects, from whom four successive pairs of blood samples were obtained at four- to five-minute intervals as follows: (1) before compression of the forearm; (2) during 20 mm. Hg pressure; (3) during 30 mm. Hg pressure; and (4) after release of the pressure. The hand circulation was occluded throughout the test. The individual results are presented in Table II, and the means in Fig. 5 (right). In every case there was a decrease in the oxygen content of the venous blood issuing from the forearm compressed at 20 mm. Hg, and a further decrease at 30 mm. Hg, resulting in an average decline in calculated blood flow of 25 and 34 per cent, respectively. Upon release of the pressure, the initial values were restored. All these changes had high statistical significance, with P values of less than 0.01. The changes in the control arm were small and not significant (P values were 0.66 to 0.79).

The average venous pressures under the compressing cuffs are shown in Fig. 6. These were determined, with the hand circulation occluded, before compression of the forearm, and at 10, 20, and 30 mm. Hg pressure on the forearm. The venous pressure under the cuffs during compression of the forearm promptly rose approximately to the cuff pressure. The indirect relationship between blood flow (estimated from the venous oxygen content) and the mean venous pressure is shown in Fig. 7.

Control Experiments: Ten control experiments were performed following the preceding procedure, with the exception that no pressure was applied to *either* forearm. Fig. 8 shows the average results, comparing the venous oxygen

TABLE II. THE VENOUS OXYGEN CONTENTS IN THE EXPERIMENTS WITH 20 AND 30 MM. HG PRESSURE APPLIED SUCCESSIVELY (METHOD II)

SUBJECT	VENOUS OXYGEN CONTENT (VOLS. PER CENT)								ESTIMATED ARTERIAL OXYGEN CONTENT (VOLS. PER CENT)
	EXPERIMENTAL ARM				CONTROL ARM				
	BEFORE PRESSURE 1	20 MM. PRESSURE 2	30 MM. PRESSURE 3	AFTER PRESSURE 4	1	2	3	4	
Wai.	9.13	7.08	5.90	9.70	10.56	10.56	9.86	9.66	16.0
McG.	13.89	13.04	11.86	14.67	13.10	13.24	12.72	13.03	19.0
Kel.	13.41	11.30	10.35	12.79	15.30	14.87	14.25	14.70	16.8
Tho.	13.07	11.75	10.83	13.55	12.25	12.94	12.78	12.90	19.3
Gor.	7.22	4.87	4.16	6.58	6.22	5.48	6.65	6.19	12.1
Mean oxygen content	11.34	9.61	8.62	11.46	11.49	11.42	11.25	11.30	16.6
Standard deviation	2.98	3.47	3.38	3.29	3.40	3.66	3.02	3.39	2.9
Mean A-V difference	5.3	7.0	8.0	5.2	5.2	5.2	5.4	5.3	
Mean hematocrit (per cent)	41.2	41.3	41.3	41.1	41.1	41.2	41.1	41.1	

contents of three successive samples taken at 4 to 5 minute intervals from the right forearm with corresponding ones from the left forearm. Little change is evident in the mean data for either side. The individual data presented in Table III, however, show that fairly large spontaneous changes in venous oxygen content did occur in many control experiments. Since the direction of the change varied from test to test, the averages remained fairly constant. The mean changes were not statistically significant, as shown by the P values of 0.26 to 0.79.

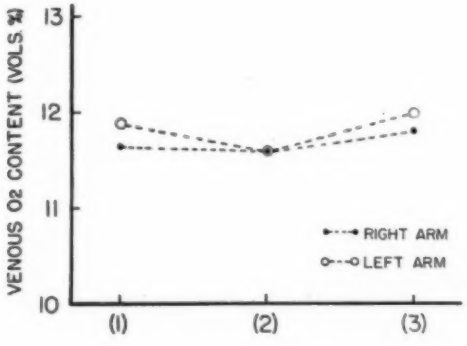

Fig. 8.—The mean results of the control experiments, showing the venous oxygen contents of three samples taken at four- to five-minute intervals from each arm. No pressure was applied to either forearm. The individual data for this group of ten subjects are shown in Table III.

TABLE III. THE VENOUS OXYGEN CONTENTS DURING THE CONTROL EXPERIMENTS—INDIVIDUAL DATA

SUBJECT	VENOUS OXYGEN CONTENT (VOLS. PER CENT)						ESTIMATED ARTERIAL OXYGEN CONTENT (VOLS. PER CENT)
	RIGHT ARM			LEFT ARM			
	1	2	3	1	2	3	
Net.	11.02	9.92	12.20	11.74	10.22	12.47	20.2
Wac.	8.18	9.53	8.39	8.40	9.23	8.66	17.5
Ben.	13.34	13.32	13.33	14.24	13.38	13.83	20.7
Cra.	10.91	11.48	10.48	10.68	10.69	10.77	20.2
Wor.	10.94	11.31	12.51	12.63	14.47	14.57	20.2
Cri.	16.22	16.65	15.94	14.60	13.63	13.89	22.8
Hat.	10.10	9.78	11.42	10.97	11.56	13.09	20.0
Jon.	12.08	12.04	9.95	12.53	11.19	10.03	21.3
Lup.	13.96	12.65	13.83	12.29	10.99	12.42	17.3
McG.	9.94	9.36	10.27	10.56	10.59	10.23	17.0
Mean oxygen content	11.67	11.60	11.83	11.87	11.60	12.00	19.7
Standard deviation	2.31	2.24	2.20	1.84	1.68	1.97	1.9
Mean A-V difference	8.0	8.1	7.9	7.8	8.1	7.7	
Mean hematocrit (per cent)	43.7	43.8	43.5	43.9	43.6	43.8	

The spontaneous changes in venous oxygen content tended to be parallel in the two arms, supporting the validity of using one arm as a control against the other in the pressure experiments. Thus, the following correlation coefficients (r) between simultaneous changes in the two arms were computed by the product-moment method: for the change from the first to the second samples, $r = +0.57$; the second to the third, $r = +0.81$; the first to the third, $r = +0.93$. (A perfect positive correlation coefficient is 1.0.)

Plethysmographic Method.—In contrast with the preceding methods, the plethysmograph provides frequent *absolute* measurements of the blood flow. Repeated determinations may be made by intermittently obstructing the venous outflow from a limb, with a blood pressure cuff just proximal to the plethysmograph. During this time blood continues to flow into the part but cannot escape, thus causing the limb to swell. The displacement of the fluid surrounding the limb in the plethysmograph is recorded on a kymograph. The rate of increase of the limb volume is measured as the rate of blood flow.

Using a plethysmographic technique previously described,[2] measurements of the amount of blood flowing to the calf of the leg combined with that returning from the foot were made before, during, and after increasing the local pressure on the foot from 30 to 60 mm. of mercury. These pressures on the foot were produced by connecting the foot plethysmograph to a bottle inflated with air at the desired pressure. Measurements were made on six subjects. Almost uniformly, the combined blood flows decreased when pressure on the foot was increased and, conversely, increased when local pressure was decreased (Table IV). The occasional erratic results were attributed to large spontaneous vasomotor variations in blood flow that characteristically occur in the foot.

TABLE IV. THE EFFECT ON THE BLOOD FLOW OF VARYING THE LOCAL PRESSURE ON THE FOOT

	PER CENT OF DETERMINATIONS		
	BLOOD FLOW INCREASED	NO CHANGE	BLOOD FLOW DECREASED
Pressure increased from 30 to 60 mm. Hg (26 determinations)	7.7	7.7	84.6
Pressure decreased from 60 to 30 mm. Hg (24 determinations)	87.5	12.5	0.0

This method has the disadvantage that it is not possible to measure directly the blood flow in the compressed area, the foot. The measured values include the blood flow to the calf, which was not exposed to the pressure. A technique was therefore developed to measure the blood flow in the forearm while pressure was applied to this segment.

The technique employed in the experiments which will be described was as follows (see Fig. 9). A standard venous occlusion plethysmograph (*A*) was fitted on each forearm in the usual way.[3] The one on the control arm was filled with water, leaving an air space of 150 c.c. which was connected directly with a recording bellows. The apparatus on the experimental arm was filled completely with water which was maintained at a temperature of 32° centigrade. To one of the lead-off holes was attached a large rubber tube (*C*), 1.5 cm. in diameter, connected at its other end with a two-liter aspirator bottle (*D*). The tube and bottle were filled with water, also leaving an air space of 150 c.c. which was connected through a rubber tube (*E*) with a second recording bellows (*F*).

Initially, the aspirator bottle was so placed that the water surface in the bottle was at the same level as that in the plethysmograph during direct recording, namely, 8.5 cm. above the center of the forearm. By raising the bottle, the hydrostatic pressure on the portion of the forearm in the plethysmograph could instantly be increased by any desired amount. Cuffs applied around the wrists just distal to the plethysmographs were inflated to a pressure greater than systolic during the determinations. Blood flow measurements were obtained by recording in the usual way the change in arm volume during inflation of the collecting cuff on the arm, just proximal to the plethysmograph. The collecting pressure was greater than that within the plethysmograph and below diastolic pressure, usually between 60 and 80 mm. of mercury. Repeated control measurements of the blood flow, as recorded through the aspirator bottle, were similar to the plethysmographic tracings obtained by the usual method from the same and the opposite arm, except for a decreased amplitude of the recorded pulse waves. The apparatus was calibrated by introducing water in 5 c.c. increments through the thermometer opening (*B*), and recording the rise of the tracing on the kymograph. The calibration was essentially the same when the aspirator bottle was elevated as when it was at the initial level, or when the plethysmograph was connected directly with the bellows.

Whenever the local pressure on the forearm was increased, the plethysmographic blood flows decreased, and, conversely, when the pressure was decreased the flows increased. A representative recording demonstrating the effect of a pressure increment of 20 mm. Hg is shown in Fig. 10.

A summary of the results and their statistical significance is presented in Table V. Immediately after a change in pressure on the forearm there was often a shift in the base line of the plethysmographic tracing, attributable to readjustment of the sealing cuffs and of the plethysmograph itself to the altered pressure. All calculations of blood flow were made on tracings taken after this effect had ceased. The table shows that even with a 10 mm. Hg increment in pressure the ensuing decrease in blood flow was statistically significant (*P* value, 0.03). With 20 and 30 mm. Hg, the statistical significance of the decrease in flow was very high (*P* values less than 0.01). The average changes in blood flow in the control arm were small, tending to be opposite in direction to those in the experimental arm, and lacking statistical significance.

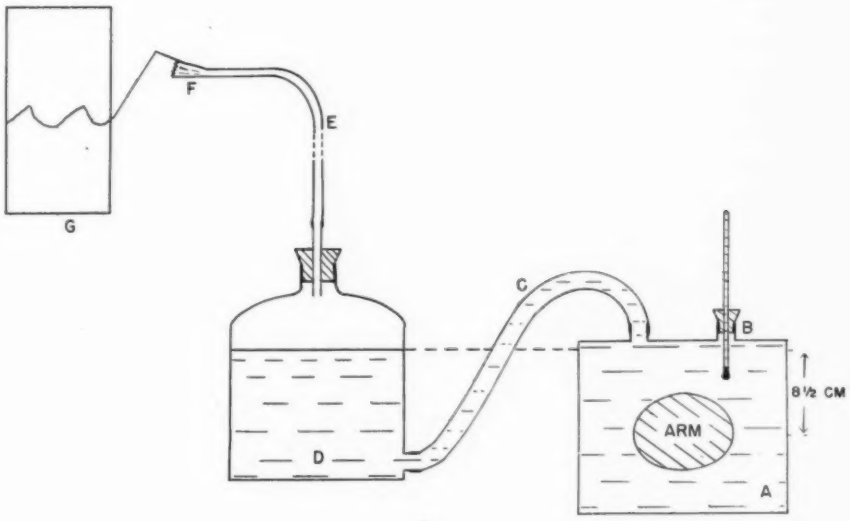

Fig. 9.—Diagrammatic representation of the apparatus used for the plethysmographic measurement of blood flow in the forearm during the application of local pressure. Symbols: *A*, plethysmograph; *B*, thermometer opening, also used for calibrating the system; *C*, 1.5 cm. bore rubber tubing; *D*, aspirator bottle; *E*, rubber tubing; *F*, recording bellows; and *G*, kymograph. By varying the height of the aspirator bottle, the desired hydrostatic pressure was applied to the segment of forearm in the plethysmograph.

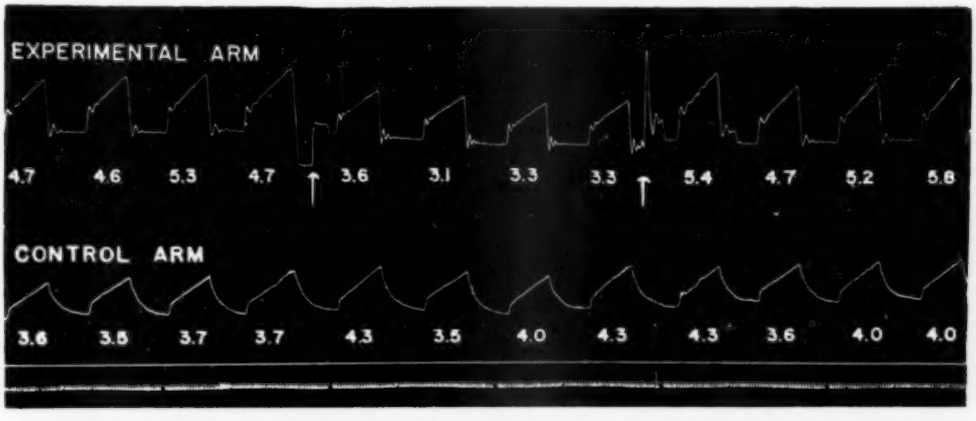

Fig. 10.—A typical plethysmographic recording of blood flow before, during, and after the application of 20 mm. Hg pressure on one forearm (upper tracing). The blood flow in the opposite (control) forearm, recorded simultaneously, is shown in the lower plethysmographic tracing. The time scale at the bottom indicates seconds.

TABLE V. THE EFFECT OF LOCAL PRESSURE ON BLOOD FLOW IN THE FOREARM—PLETHYSMOGRAPHIC DATA

ITEM			10 MM. HG INCREMENT IN PRESSURE (7 EXPERIMENTS)		20 MM. HG INCREMENT IN PRESSURE (11 EXPERIMENTS)		30 MM. HG INCREMENT IN PRESSURE (7 EXPERIMENTS)	
			EXPERIMENTAL ARM	CONTROL ARM	EXPERIMENTAL ARM	CONTROL ARM	EXPERIMENTAL ARM	CONTROL ARM
Blood flow in c.c. per minute per 100 c.c. of forearm	Before pressure	Mean	2.96	2.83	2.97	2.65	3.10	2.69
		S.D.	0.77	0.76	0.92	0.65	1.08	0.85
	During pressure	Mean	2.69	3.07	2.16	2.94	1.53	2.89
		S.D.	0.83	1.01	0.70	1.05	0.56	0.81
	After pressure	Mean	3.25	2.90	3.10	2.87	3.01	2.89
		S.D.	0.73	0.96	1.11	1.07	1.12	0.74
Statistical significance of changes in blood flow	On applying pressure	Mean change	−0.28	+0.24	−0.81	+0.29	−1.57	+0.20
		P*	0.03	0.13	<0.01	0.15	<0.01	0.09
	On removing pressure	Mean change	+0.56	−0.17	+0.94	−0.07	+1.49	0.00
		P*	<0.01	0.27	<0.01	0.11	<0.01	0.91

*P is the probability that the change is due to chance. Values of 0.05 or less indicate statistically significant changes.

These results could not be compared directly with those of the blood gasometric method for the following reasons. In the latter method the initial pressure on the arm was zero (atmospheric). This was not true in the plethysmographic method, where the initial pressure was 8.5 cm. H_2O (or 6 mm. Hg), to which the various increments in pressure were added. It was necessary, therefore, to estimate by graphic extrapolation the blood flow at zero pressure, and by interpolation the flows at 10, 20, and 30 mm. Hg above atmospheric. The way in which this was done is shown in Fig. 11, where the blood flows, in terms of the initially measured rate (which was given an index value of 100), are plotted against pressure *above atmospheric*. The extrapolated blood flow at zero pressure was thus 106, and the interpolated flows at 10, 20, and 30 mm. Hg pressure above

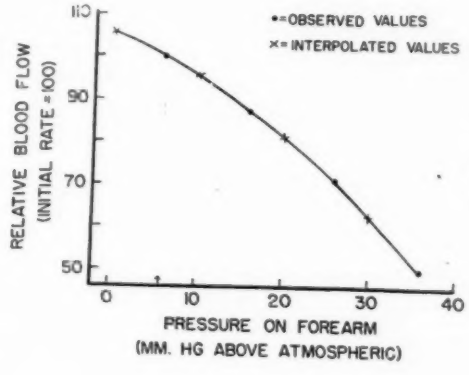

Fig. 11.

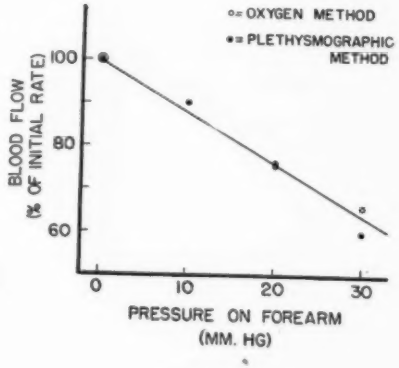

Fig. 12.

Fig. 11.—Graphic interpolation of plethysmographic blood flows at true pressures (related to atmospheric pressure) of 0, 10, 20, and 30 mm. of mercury. The arrow on the horizontal scale, at 6 mm. Hg, denotes the mean hydrostatic pressure at which the initial blood flow measurements (given an index value of 100) were made, and to which the various pressure increments were added. The observed values were calculated from the data in Table V.

Fig. 12.—A comparison of the effect of local pressure on the blood flow in the forearm by the blood gasometric (Table II) and plethysmographic methods. The blood flow at zero (atmospheric) pressure is given an index value of 100 in each case.

atmospheric were 95, 81, and 63, respectively. Therefore, at 10 mm. Hg above atmospheric the blood flow was reduced to 95/106 = 90 per cent of that at zero pressure; at 20 mm. Hg, to 81/106 = 76 per cent; and at 30 mm. Hg, to 63/106 = 60 per cent. As shown in Fig. 12, these values were approximately equal to those calculated from the venous oxygen method on the assumption that the rate of oxygen utilization remained constant. This finding confirms that assumption.

DISCUSSION

While it was obvious that a reduction in blood flow would occur in an extremity during local compression of considerable degree, it was not known how little compression is necessary to produce this effect. The problem had already

been partly investigated by Darling and Belding,[1] whose purpose was to evaluate the role of pressure by foot gear in the development of trench foot. Their method consisted of measuring the skin temperature of various parts of the foot while the subject was in a cold room (0°F. or 4° F.). They found that when a pressure of 50 mm. Hg or more was applied to one foot by means of a pneumatic stocking, it cooled more rapidly than did the opposite foot, which was not compressed. No consistent differences were obtained with pressures lower than 50 mm. of mercury. The authors indicated, however, that their method may not have been sufficiently delicate to detect small changes in blood flow, and also that the intense vasoconstriction in the cold environment may have masked the effects of lower pressures.

In the present study it was shown that increments in local pressure as small as 10 mm. Hg were sufficient to reduce definitely the circulation in normal limbs. These results, obtained by three different methods, demonstrate the importance of small degrees of local compression. Thus, pressure on the extremities, such as those ordinarily produced by snug clothing, gloves, shoes, bandages or splints, or by the weight of the limbs themselves, or even of the bed clothes upon the bony prominences may be sufficient to reduce significantly the circulation in the compressed parts of normal limbs. In patients with peripheral vascular disease, such reduction of blood flow may produce serious results. The importance of these findings both in medical and surgical cases seems obvious.

The mechanisms by which blood flow is reduced during local compression are interesting to speculate upon. Certainly, one factor is the reduction of the pressure gradient between the arteries and veins as demonstrated by the prompt rise in venous pressure approximately to that in the compressing cuffs. Another possible mechanical factor involved in the reduction of blood flow is the decrease in the caliber of the small vessels in the compressed area causing an increase in resistance to flow.

SUMMARY

The effect of locally applied pressures of 10 to 50 mm. Hg on the extremities was investigated by three methods: (a) thermometric; (b) blood gasometric; and (c) plethysmographic. The results indicated that local pressures of remarkably low amounts may impair the circulation. Skin temperature measurements showed a definite effect with pressures as low as 20 mm. of mercury. At this pressure, the arteriovenous oxygen difference rose about 25 per cent, and plethysmographic tracings showed an equal decline in blood flow. With a local pressure of 30 mm. Hg, the blood flow decreased about 25 per cent as measured both by the blood gasometric and the plethysmographic methods. Even at 10 mm. Hg the plethysmograph revealed a 10 per cent decline in blood flow.

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THE FUNCTIONAL PATHOLOGY OF EXPERIMENTAL IMMERSION FOOT

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THE abundant literature on trenchfoot and frostbite which appeared after the first World War, and especially after the second World War, is full of contradictory statements. Those students of the subject who go somewhat deeper into the question of the functional pathology of the two lesions, or as many authors like to state, one lesion, can be divided into two opposing groups. One group, under the leadership of Ungley and Blackwood,[1] feels that in the immersion foot syndrome all lesions due to cold, including frostbite, are due mainly to a peripheral vasoneuropathy, almost all of the pathology being located in the muscle and nerve tissue. The other group, under the leadership of Greene,[2] Friedman,[3] and Siegmund,[4] believes that the lesions of frostbite, as well as of immersion foot syndrome, are caused by intravascular agglutinative thrombi as we[5,6] and others have demonstrated in actual cases of frostbite and in experimental frostbite.

Kreyberg,[7] with his deep understanding of the functional pathology of the lesions due to cold, tries to differentiate clearly between the lesions due to moderate but protracted cold in a wet surrounding (immersion foot) and the lesions due to intense but short-lived exposure in a surrounding of air (frostbite). All conclusions concerning immersion foot are drawn from analogy, as Kreyberg[7] states, since actual observations during the exposure and immediately thereafter are almost completely missing and since the biopsy material is confined almost exclusively to gangrenous areas.

We felt, therefore, that it is essential to produce trenchfoot in experimental animals to permit the study of the functional pathology and to determine whether therapeutic measures such as heparinization, which we found successful in frostbite, are applicable to trenchfoot lesions. There is only one report in the literature, by Smith and associates,[8] in which an attempt was made to produce trenchfoot experimentally and their results were rather doubtful.

After numerous difficulties, we were able to produce in rabbits a constant lesion comparable to immersion foot (Fig. 1).

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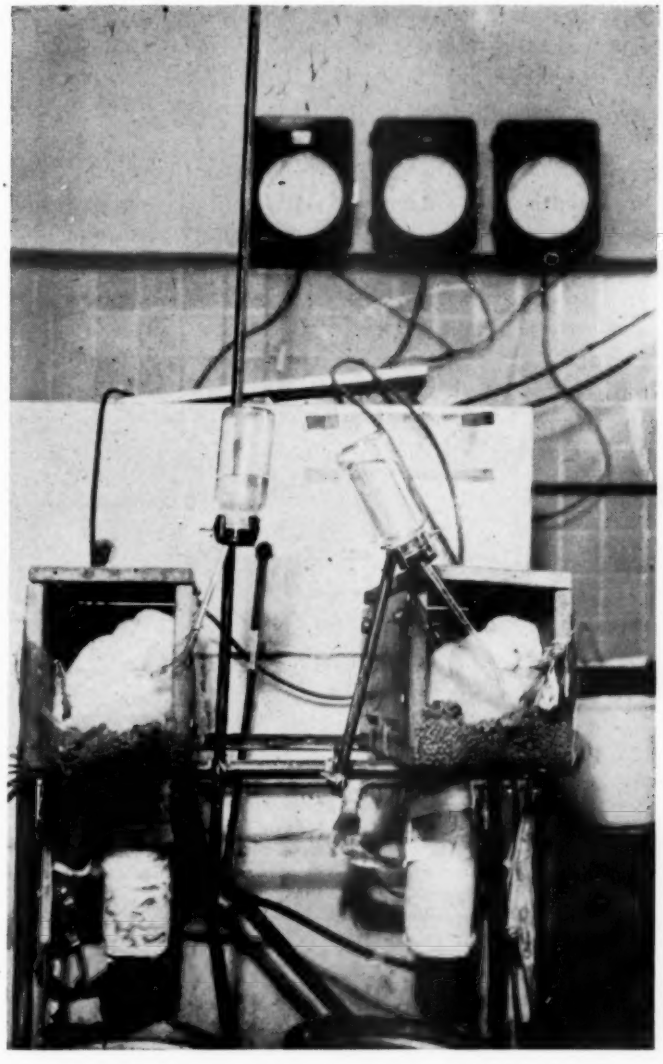

Fig. 1.—Two rabbits in experimental setup for the production of trenchfoot. The cylinder from the right foot is removed to make the position of the animal visible.

EXPERIMENTAL METHOD AND OBSERVATIONS

A female adult rabbit is placed in a rabbit box with both hind legs projecting through holes in the floor and into two aluminum cylinders fastened to the bottom of the box. The left cylinder is closed at the bottom except for an inlet for water, and has an outlet near the top. Water constantly enters this cylinder containing the left hindleg of the rabbit from a tube, which siphons it from a reservoir through coils into the cylinder and is removed through the outlet by a pump which returns it to the reservoir. The coils are placed in the tank of a cooling unit which per-

mits an exact control of the temperature of the water entering the cylinder. A recording thermometer in the cylinder records the temperature of the water throughout the experiment. The temperature does not vary more than 2°F. during the entire exposure. The animals are prevented from escaping by two straps holding them down in the box.

All experiments last for three to four days, during which time the animals are fed and watered unless starvation is part of the experiment. The rectal temperature, respiratory rate, and electrocardiogram are taken at regular intervals. The opposite leg is not cooled but held in a similar cylinder without water to see the effect of immobility and dependency. Thermocouples are inserted into the exposed leg during the exposure in certain experiments.

At temperatures between 3 and 5° C., one is able to make the following observations: After immersion, the temperature of the exposed limb goes down rapidly but does not reach the temperature of the surrounding water even after several days, indicating the persistence of some circulation in the limb (Fig. 2). If fluor-

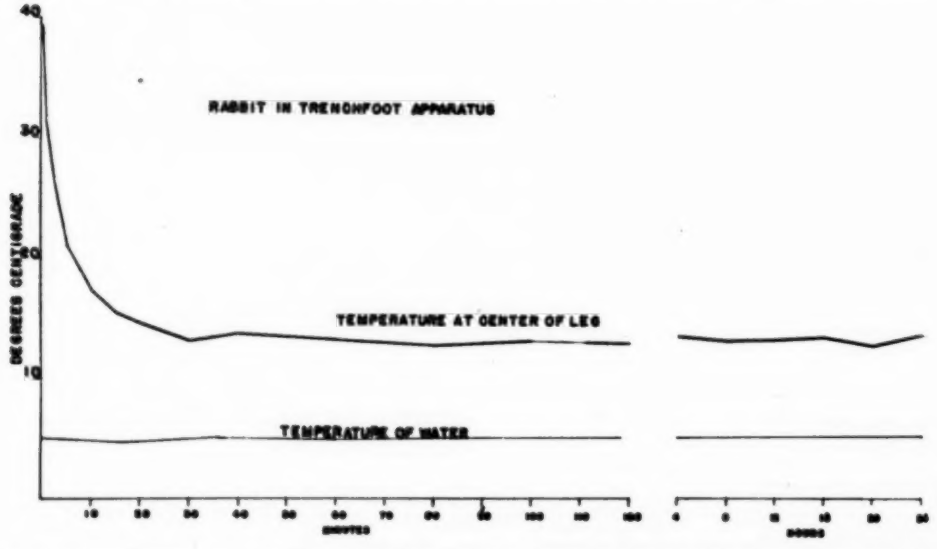

Fig. 2.—Temperature near the tibia of the left calf in a rabbit in the trenchfoot apparatus and the temperatures in the water surrounding this leg.

escein is given into the ear vein one will notice that, in contrast to exposures to subzero temperatures, as in frostbite, the dye always appears in the exposed limb, although markedly delayed and in lower concentration compared with the nonexposed limb. Severe swelling occurs *during* the exposures; it is quite noticeable after twenty-four hours, and is severe after forty-eight hours of exposure. It extends all through the exposed part of the limb. The appearance of swelling *during* the exposure is in direct contrast to frostbite, where the swelling occurs *after the end* of the exposure. This, again, indicates that during the immersion the circulation is not completely interrupted, for only in the presence of a positive filtration pressure in the vascular system can edema occur. The nonexposed leg

Fig. 3.—Severe swelling of left calf and toes of a rabbit exposed for ninety-six hours to water at a temperature of 3° centigrade. One day after exposure.

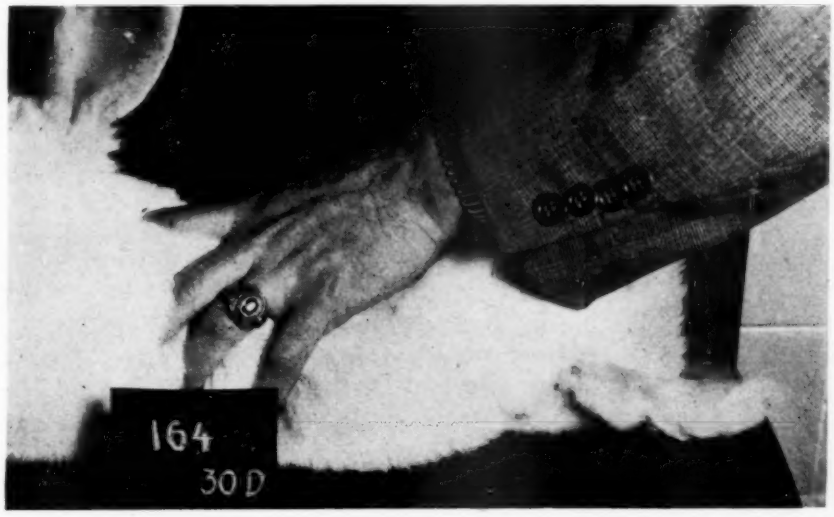

Fig. 4.—Rabbit thirty days after exposure of the left leg for ninety-six hours to a temperature of 3° centigrade. Note dragging of the left leg.

also shows some swelling due to the dependency, but this is present only over the toes and is not of the same order of magnitude as the swelling in the exposed leg. When removed from the device after three days of exposure, the temperature in the depth of the exposed leg rises immediately and rapidly, reaching body temperature within thirty minutes. The leg is severely swollen and the animal is unable to use the leg due to a flaccid paralysis. Muscular tone has disappeared; passive movement is possible without resistance, pinprick produces no reaction and the leg is dragged (Figs. 3 and 4). A fluorescein test performed at this time shows maintenance of a slow but positive circulation. After three to six hours, the leg becomes markedly hyperemic and hot. A fluorescein test[9] performed at this time shows a marked hyperfluorescence due to the increased capillary permeability.

After forty-eight hours the swelling of the leg has disappeared, the hyperemia has become moderate, and the hyperfluorescence has decreased. The swelling over the toes in the nonexposed leg disappears within four hours after the end of the exposure. The exposed foot is dropped when the animal is lifted up and the animal is apparently unable to spread its toes, leading to a characteristic appearance of the foot (Fig. 5). There is no reaction to pinprick or tapping of the Achilles tendon. The animal cannot use this leg and drags it when walking. All of these signs persist for from four to ten weeks in most animals. They are usually combined with a marked atrophy of the muscles of the foot and the calf. The characteristic foot drop and the inability to spread the toes are the most persistent signs. This inability to spread the toes is also a very characteristic and persistent sign of human trenchfoot lesions. The animals favor the opposite leg for many weeks although the skin has returned completely to normal. The regrowth of the clipped hair is not slower on the exposed side than on the nonexposed side (Fig. 6). The circulation time and capillary permeability return to normal in four to five days and the reaction to pinprick usually returns after four to five weeks.

It was most astonishing that of the seventy-five animals subjected to the exposure, of which twenty-eight survived the seventh day after exposure, none showed any gangrene except in areas of superimposed trauma or infection.

In order to exclude the water without the lowered temperature as the cause of the swelling and the muscular and neurological phenomena, the legs of five animals were exposed in the cylinder to water at body temperature. They showed a fleeting swelling similar to that found in the legs with dependency only, but after twenty-four hours, there is complete restitution of normal function and shape of the leg.

Morphologic studies of the limbs of animals sacrificed at varying intervals are being carried out* and will be reported in the near future. One thing is outstanding, however: in none of the specimens of trenchfoot animals of any stage can one discover the agglutinative thrombi of red cells which are so characteristic of true frostbite. The histologic lesions seem to be confined to the muscles and predominantly to the nerve tissue, in which severe degenerative changes can be

*In collaboration with Dr. N. B. Friedman of the Army Institute of Pathology.

found for weeks following the exposure. There is an excellent correlation between the nerve lesions and the functional disturbances. They are completely different from the lesions seen in frostbite.

It is, therefore, obvious that the treatment by heparinization for six to ten days which we described to prevent gangrene subsequent to frostbite is not applicable in trenchfoot. It should be mentioned here that in frostbite the heparinization has to be continuous and persistent. The failure to obtain results recently reported by Quintanilla and associates[10] was due to heparinization for only thirty-six hours.

Fig. 5.—Foot drop and inability to spread the toes in the left leg of a rabbit. The leg was exposed for ninety-six hours to a temperature of 3° centigrade. Three days after exposure.

It is interesting to speculate as to the actual cause of the lesions in trenchfoot. By introducing a thermoneedle into the vein carrying the blood from the exposed leg, one notices that the temperature of this blood is almost identical with the internal temperature of the exposed leg. At a temperature of 6° to 8° C., however, the oxygen dissociation of the blood is extremely low.[14] Although

one can assume that the tissue metabolism is also at a very low level, the fact remains that there exists almost complete tissue anoxia for as long as several days. The slow speed of the blood stream in such a limb contributes further to the anoxia. The blood returning from such a limb is bright red and shows no apparent oxygen depletion. The skin of the leg itself appears bright pink due to the lowered dissociation. In order to see whether these factors lead to a local histamine production which, in turn, produces the increased capillary permea-

Fig. 6.—Same animal as in Fig. 5 three weeks after exposure. Note the same neurological lesions but the extensive regrowth of hair.

bility, we kept two animals on high doses of pyribenzamine during the entire length of the experiment. They did not show any diminution of swelling as compared to the other animals. The fluorescein tests done during the first twenty-four hours after exposure indicate an increase in permeability in the exposed as compared with the nonexposed side. This increase is, however, much less intense than that seen after exposure to frostbite; it is less intense as well as less

persistent. It is, therefore, understandable that the loss of plasma which leads to the typical stranding of red cells and the silting up of the capillaries with subsequent agglutinative thrombi in frostbite cannot be found in trenchfoot and that, therefore, the subsequent intravascular phenomena are missing.

Of our group of seventy-three animals thus exposed, eight showed a marked lowering of body temperature twenty-four to seventy-two hours after the onset of exposure. It appeared that in the face of the continuous heat withdrawal from the one leg, they were not able to maintain their body temperature. In these animals a typical sequence of events occurred.

At first, when the body temperature has dropped to 32° to 33° C. the pulse rate rises, the animals become very irritable, and seem to have an unstable gait when taken out of the box. Further slow lowering of the body temperature to approximately 28° C. produces considerable drowsiness. The respiration and the pulse rate become progressively slower until death occurs at a body temperature of approximately 24° centigrade.

During the last phase of lowered temperature, between 24° and 28° C., marked electrocardiographic changes may be found. Deep depressions of the S-T segments in all leads are followed by an elevation of the S-T segments with inverted T waves as seen in myocardial infarctions (Fig. 7). Morphologic ex-

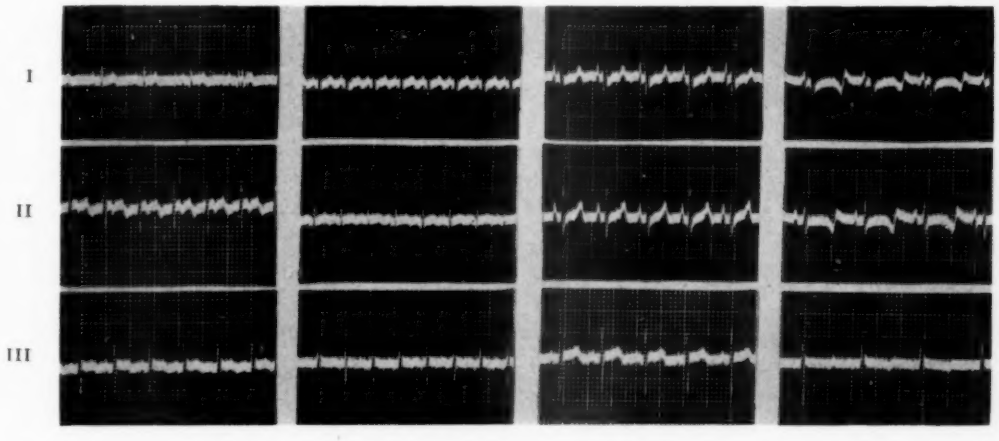

Fig. 7.—Electrocardiograms of a rabbit during trenchfoot exposure with general loss of body temperature.

aminations of such hearts, however, have thus far failed to reveal any specific lesion. In two animals we succeeded in promptly reversing these electrocardiographic changes by rapidly raising the body temperature by means of hot baths and warm saline enemas. Nevertheless, these animals died.

These findings, which require further study, may explain certain cases described in the German,[11] British,[12] and recently, in American literature,[13] in which survivors of shipwreck showed marked disturbances in cardiac rhythm,

and sometimes sudden death during an apparently uneventful recovery. The mechanism may possibly be explained by the prolonged myocardial anoxia produced by the diminished oxygen dissociation. It is possible that we have seen more of such disturbances than other observers, since our experiments lead to a slow and gradual lowering of body temperature whereas other observers were using experiments directed toward an acute, rapid lowering of body temperature.

SUMMARY AND CONCLUSIONS

In conclusion, we wish to state that the lesions in experimentally produced trenchfoot are basically different from those in frostbite. They consist mainly in disturbances of muscular and nervous function. Intravascular agglutinative phenomena characteristic of frostbite are missing.

In contrast to frostbite, the circulation in the exposed limb continues during the immersion, although it is slower and diminished in amount. Edema in trenchfoot occurs, therefore, *during* the exposure whereas in frostbite it occurs some time *after* the exposure.

The increase in capillary permeability is much milder in trenchfoot than it is in frostbite.

Gangrene subsequent to experimental trenchfoot lesions is extremely rare and occurs only when pressure or local infection are superimposed.

The lesions in trenchfoot seem to be a consequence of the protracted tissue and especially nerve anoxia, while in frostbite the main part of the damage is due to intravascular agglutinative thrombi.

The tissue anoxia due to lowered oxygen dissociation seems also to be the cause of severe electrocardiographic changes in animals in which the body temperature is lowered due to the trenchfoot exposure.

It is possible and even probable that the two lesions may overlap or coexist in individuals exposed to sudden extreme cold during a long exposure to immersion foot conditions, or in individuals who have a great tendency to vascular spasm. Such individuals may react with a complete vascular shutdown, as seen in frostbite, when normal individuals still maintain a certain amount of circulation. Usually it is the extreme cold, with complete circulatory standstill in the exposed part, which causes the severely increased capillary permeability leading to stranding of the red cells in the capillaries.

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THERAPY DIRECTED AT THE SOMATIC COMPONENT OF CARDIAC PAIN

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THE idea that visceral pain may be relieved by local anesthesia of the somatic tissues concerned in the reference of pain is not new. Nearly twenty years ago this fact was demonstrated by Weiss and Davis[1] in twenty-five cases of visceral disease, which included two of heart disease. However, the therapeutic import of their observations became lost in the issues which developed as to the theoretical role of the so-called "somatic reference zone" in the mechanism of visceral pain reference.

We likewise have found that local block of afferent neural impulses from the somatic structures which mediate referred visceral pain may relieve pain due to heart disease under suitable conditions.[2] This report deals with the demonstration of this fact, and with practical aspects of local block therapy directed at the somatic component of cardiac pain.

CLINICAL DATA

We have studied thirty-one patients with chest pain due to coronary artery disease, who presented trigger areas in the voluntary muscles, and in whom an attempt was made to block the noxious impulses from these abnormal foci either by local procaine infiltration or by ethyl chloride spray. These observations on pain of cardiac origin have been oriented against a background of experience in a larger number of patients with chest pain and somatic trigger areas activated by disorders of the skeletal muscles rather than by heart disease.

The common denominator of cardiac and somatic chest pain in these subjects is the presence of a trigger mechanism in the somatic structures. It is, therefore, necessary first to define the abnormal zone of hypersensitivity known as a trigger area. Its essential characteristic is that when it is stimulated by pressure or needling, it gives rise to a brief reference of pain. The referred pain is usually perceived at a distance from the trigger area, but as in the case of the precordial muscles, it may circumscribe the trigger area itself.[3,4] In either case, the spread of pain represents a true reference phenomenon, since it does not conform to an area supplied by a peripheral nerve.

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The distribution of pain referred from trigger areas is relatively constant for the site of origin; thus, similarly located trigger areas in different individuals produce similar, and therefore, predictable pain reference patterns.[5,6] As a consequence, in skeletal muscle disorders without organic heart disease, the appropriate trigger areas give rise to referred pain which is indistinguishable in distribution and quality from the substernal and radiating pain of coronary insufficiency.

Although trigger areas reside occasionally in the skin, we have found them to be located in most instances within the myofascial structures. It is not known what tissue within the muscle mass becomes physiologically altered so as to constitute the trigger area, but we have observed that in the process of biopsy of a trigger area without anesthesia (except morphine), lightly touching, lifting, or pinching the outer fibrous sheath of the muscle at this spot momentarily reproduced the specific pattern of pain reference which characterized this trigger area and which had been previously elicited by pressure.

LOCATION OF TRIGGER AREAS

Muscles which frequently develop trigger areas in association with coronary artery pain are the pectoralis major and minor and the serratus anterior. The patterns of referred pain induced by mechanical stimulation (needling) of trigger areas in these and other muscles of the chest and shoulder girdle have been mapped both in the presence and absence of heart disease. As has been implied, the patterns are similar whether the trigger mechanism is activated by cardiac or somatic factors.

It has been found that trigger areas in the myofascial structures of the parasternal region give rise to pain perceived chiefly beneath the sternum. Trigger areas in the lateral part of the precordium, where the pectoralis major and minor muscles overlap, give rise to pain widely distributed over the precordium, occasionally referred to the scapula and frequently to the medial epicondyle of the elbow and ulnar distribution in the forearm and hand. Trigger areas in the inferior margin of the pectoralis major muscle at its mid-point include the nipple and breast in their reference pattern. Trigger areas close to the ribs in the lowest slips of the pectoralis minor muscle at their origin often produce pain located deep within the chest and described as "inside the heart." Trigger areas anterior to the sternum in the rudimentary sternalis muscle give rise to a reference of pain which may extend up and down from the base of the neck to the epigastrium. Trigger areas in the axillary region in the serratus anterior muscle induce a spread of pain at the corresponding level which travels anteriorly almost to the sternal border and posteriorly as far as the interscapular line, and occasionally to the volar aspect of the arm as far as the palm. Trigger areas in the serratus muscles are apt to cause pain on deep inspiration, or a sense of constriction of the chest.

With a precise knowledge of these reference patterns, the search for trigger areas is facilitated if the patient gives a clear description of the location of spontaneous pain. However, the essential part of the examination is the discovery by careful palpation of discrete areas of exquisite tenderness. Thus, the examiner

may suddenly locate a small spot of hyperalgesia so acute that the patient winces when it is palpated. The hyperalgesia may be cutaneous, but usually it represents a hypersensitivity of the deeper structures. This is shown by the fact that the skin may be lifted off the deeper structures and compressed without inducing pain, whereas even light pressure against the skin when it is in contact with the underlying structures elicits a painful response.

When an extremely sensitive trigger area is stimulated by pressure, the patient usually describes a reference of pain clearly perceived at a distance. On the other hand, if the spread of pain induced by pressure circumscribes the trigger area, the subject may fail to distinguish the reference of pain from the local hyperalgesia at the trigger area itself. With the stronger stimulus of needling the trigger area, however, the reference pattern is usually sharply delineated.

LOCAL BLOCK TECHNIQUES

Local Infiltration.—Since the relief of pain by so-called "analgesic" injection is not dependent on the local anesthetic action of a drug,[7] the concentration of procaine hydrochloride in physiologic saline has been reduced for infiltration to 0.25 to 0.5 per cent. One reason for using any procaine at all is that even such low concentrations appreciably reduce the immediate pain induced by the infiltration.

The patient is questioned regarding sensitivity to procaine, and if a history of allergy is obtained or if the patient has never before received procaine, either physiologic salt solution is used for injection, or an initial test dose of 5 to 10 mg. of procaine hydrochloride is given by muscle and the patient observed for ten minutes for a general reaction. The total dose of procaine hydrochloride at the first treatment is limited to 100 mg. and is stepped up gradually at subsequent treatments if necessary. If the patient is unduly apprehensive and has not received previous sedation, a preliminary dose of a rapidly acting barbiturate is given by mouth.

In infiltrating trigger areas in the muscles, it is not necessary to infiltrate the skin. There is also no need to withdraw on the plunger of the syringe to determine whether the point of the needle lies within a blood vessel if dilute solutions of procaine are used and if infiltration is performed with the needle constantly moving in or out. The needle is kept in motion in order to reach as many muscle layers as possible, and also to avoid introducing more than a drop or two of the procaine solution into a blood vessel, if one were entered. Furthermore, the intravenous injection of procaine in the nonallergic individual no longer connotes the same hazards as formerly, and is being widely used by this route in a variety of clinical conditions.[8,9]

The depth of injection depends on the site of the trigger area. At the sternal borders, the musculature is thin and the trigger areas therefore superficial. Laterally, the pectoral muscles are thicker and the trigger areas may be fairly deep, especially where the thoracic cage falls away from the skin surface. Therefore, in a muscular person it may require a two inch needle (23 gauge) to infiltrate a trigger area in the pectoralis minor muscle. For more superficially located

trigger areas in the pectoralis major and serratus muscles, a one to one and one-fourth inch needle (24 gauge) is used. The needle should not be inserted up to the hilt because of the difficulty of extraction in case of breakage. It should be inserted at a tangent to the ribs to assure that the pleural cavity is not penetrated.

For a given trigger area the amount of solution injected is usually about one to four cubic centimeters, but less may suffice. If local tenderness at the trigger area is not abolished, reinjection of the same area at a different depth or angle is employed.

Pyrogen-free solutions are used. When pyrogenic materials are injected into trigger areas, intense afterpain may result.

Ethyl Chloride Spray.—A technique somewhat modified from that recommended for sprains[10] is employed. A standard glass container, preferably with a nozzle which delivers a fine spray, is used. The tube is held about two feet from the patient. The spray is applied not perpendicularly, but at an acute angle or even at a tangent to the surface of the skin. It is applied with a constant rotary motion of the wrist so as not to concentrate it in a small area. The spray is usually applied for about five to fifteen seconds at a time; it is discontinued if the skin becomes blanched. Frosting is to be avoided; if frost appears, it is promptly wiped off.

To avoid inhalation of ethyl chloride vapor, an adequate circulation of air is desirable. Since the vapor is heavy and travels downward, it is preferable that the spray should be applied with the patient sitting up, or at least propped up with pillows. The usual precautions for the handling of a volatile inflammable substance should be observed.

Spraying is continued at brief intervals until the spontaneous pain has disappeared. If pain persists, this procedure is stopped after about ten to fifteen minutes.

If ethyl chloride spray fails to relieve pain, local infiltration of the trigger areas may be tried. One should, however, await the return of the skin to room temperature because ecchymosis has followed immediate needling of a heavily sprayed area.

RESULTS

The thirty-one subjects with pain due to inadequacy of the coronary circulation were classified into three groups: Group 1, subjects with constant chest pain initiated by an acute myocardial infarct and no pain prior to this event (four patients); Group 2, subjects with effort angina associated with antecedent or intercurrent myocardial infarction (eighteen patients); and Group 3, subjects with effort angina uncomplicated by a known myocardial infarct (nine patients). We shall omit from consideration the results of local block therapy in those other patients with chest pain who had equivocal or no evidence of coronary artery disease.

Patients With Constant Chest Pain.—The patients in Group 1 provided the most convincing demonstration that cardiac pain may be blocked at the somatic

component. Table I shows the results obtained in four subjects who had five myocardial infarcts and prolonged substernal or precordial pain following each of these events, but no anginal pain previously. The duration of pain prior to treatment ranged from four hours to twenty-one days. One of these patients (I. C.) had marked hypertension (200/110).

Complete relief of the protracted pain was secured in all instances, either by local procaine infiltration of the trigger areas in the precordial muscles, or by ethyl chloride spray of the discrete tender areas in the precordium, or by a combination of both procedures. In four infarctions, complete relief was immediate, and one treatment sufficed to secure a permanent result. In one infarction, temporary amelioration of pain occurred after the first local block, but four such treatments were necessary to obtain lasting complete relief.

Two of these cases with persistent chest pain following acute myocardial infarction are presented in detail. (Cases 1 and 2.)

TABLE I. RESULTS OF LOCAL BLOCK THERAPY IN CONTINUOUS CHEST PAIN INITIATED BY A MYOCARDIAL INFARCT

PATIENT	SEX AND AGE	DURATION OF PAIN PRIOR TO THERAPY	TECHNIQUE FOR BLOCK	NO. OF TREATMENTS	RELIEF OF PAIN	DURATION OF RELIEF
W. T.	M 73	7 hours	Procaine infiltration	1	Complete	2 years (until next infarction)
	M 75	12½ hours	Procaine infiltration	1	Complete	1½ years (to date)
L. Lu.	M 52	23 hours	Ethyl chloride spray	1	Complete	7 months (to date)
I. C.	M 67	21 days	Procaine infiltration	1	Complete	9 months* (to date)
L. Le.	M 46	4 hours	Procaine infiltration and ethyl chloride spray	4	Partial until 7th hospital day, then complete	7 months (to date)

*Precordial chest pain for about two hours during each of two attacks of acute left ventricular failure with pulmonary edema four and six months, respectively, after infarction.

Patients With Effort Angina (Groups 2 and 3).—The difficulties in evaluating any form of treatment in chronic cardiac pain are well known. However, analysis of the results of local block of the somatic component in the eighteen patients of Group 2 with both effort angina and myocardial infarction indicates that this procedure may be effective when the anginal syndrome appears soon after an acute myocardial lesion. Of twelve patients with this type of onset, all received significant relief of both the severity and frequency of anginal attacks, as indicated by increased physical activity and decreased use or discontinuance of nitrites. These patients received an average of about six treatments by local procaine infiltration given at weekly, or occasionally, at biweekly intervals. Ethyl chloride

spray was employed in only one patient; in this patient, numerous trigger areas were present in the skin as well as in the deeper structures. In three of the twelve patients with postinfarction onset of pain, the effort angina was completely abolished by local block therapy even when normal activity was resumed (three, four, and four months of observation after treatment, respectively); effort angina had been present since infarction for four, three, and one and one-half months, respectively. In one case in which anginal pain had been present for as long as ten years since myocardial infarction, marked relief was secured by local infiltration. A long duration of chest pain, therefore, does not preclude a good result in these postinfarction anginal syndromes.

The results in these twelve patients of Group 2, the onset of whose effort angina followed infarction, are to be contrasted with those obtained in the remaining six patients in this group, in whom the anginal syndrome antedated the first myocardial infarct and in whom local block therapy was instituted some time after infarction. In these patients with effort angina of gradual onset, persistent treatment extending even over many months afforded at the best only partial relief, and the anginal syndrome reverted to its previous severity soon after local block therapy was discontinued. These relatively unsatisfactory results are similar to those observed in the nine patients of Group 3 with effort angina of insidious onset, but without acute myocardial infarction.

On the basis of the response to local block therapy, the fifteen patients (six of Group 2 and nine of Group 3) with effort angina of insidious onset appear to represent one class, irrespective of whether infarction occurred intercurrently or not. The therapeutic result in this group is so different from that noted previously in the twelve patients with postinfarction onset of effort angina that various factors have been analyzed to insure that these represent comparable groups. As shown in Table II, the proportion of men was high in both, namely, 87 per cent in the former and 75 per cent in the latter. The average ages were 58 and 59 years, respectively, with almost identical ranges. Marked hypertension was present in 33.3 and 25 per cent, respectively; this difference is not considered statistically significant. In the patients with angina of insidious onset, the duration of anginal pain prior to therapy ranged from four weeks to eight years, as compared with six weeks to ten years in the patients with angina precipitated by infarction. In conclusion, it may be stated that except for the

TABLE II. ANALYSIS OF FACTORS IN EFFORT ANGINA WITH DIFFERENT MODES OF ONSET

ONSET OF PAIN	NUMBER OF PATIENTS	NUMBER OF MEN	AVERAGE AGE (YEARS)	HYPERTENSION		AVERAGE RESPONSE TO LOCAL BLOCK
				NUMBER	PER CENT	
Post infarction	12	9	59 (43-65)	3	25	Good
Gradual	15	13	58 (42-72)	5	33.3	Poor

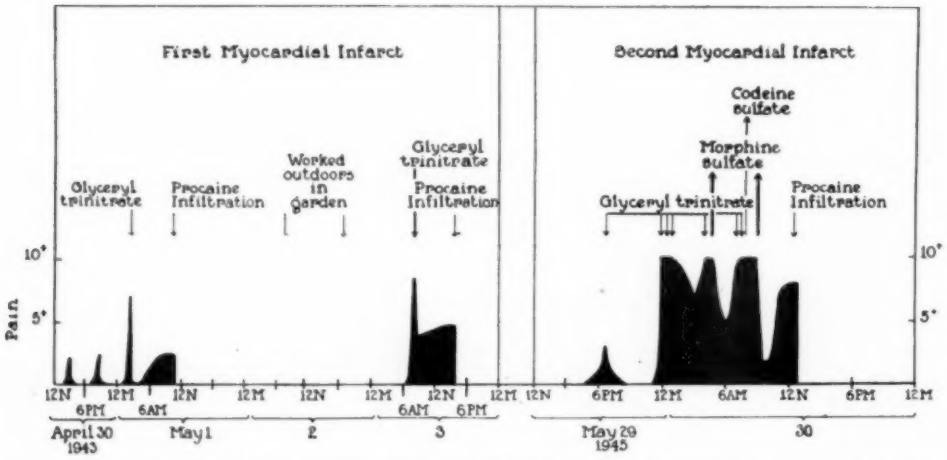

Fig. 1.—Case 1. Influence of medication and of local procaine infiltration on pain for the first and second myocardial infarction two years apart. An arbitrary scale has been adopted to indicate relative intensities of pain.

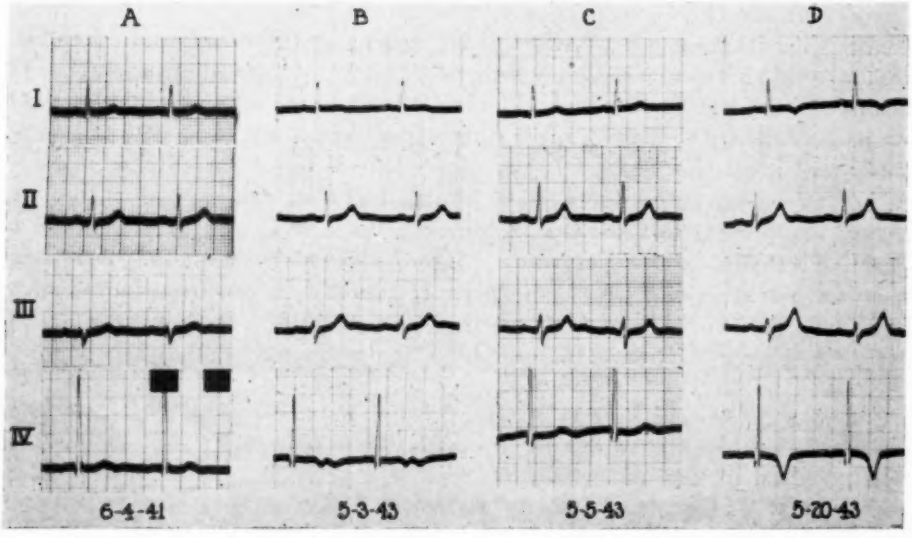

Fig. 2.—Case 1. First infarction. Serial changes of a recent myocardial infarct. *A*, Routine tracing taken two years prior to the first infarct. Normal record. *B*, Record taken seven hours after onset of protracted pain and just prior to procaine infiltration. Note abnormal T_1 and T_4. *C*, Record taken two days after complete relief of pain by procaine infiltration. T_1 and T_4 have now returned to normal. *D*, Record taken about two weeks later showing change characteristic of an anterior wall infarct.

type of onset of effort angina, no important differences could be discovered in these two groups.

One of the cases with complete relief of anginal pain after local block of the somatic component is reported (Case 3).

ILLUSTRATIVE CASES

CASE 1. *Block by Local Infiltration in Acute Myocardial Infarction.*—

First Myocardial Infarct: On April 30, 1943, when 73 years old, W. T., a white male physician, experienced brief substernal and precordial pain once during the afternoon and once during the evening. This was the first time he had ever had chest pain. During the night he was awakened by a severe attack of substernal pain which radiated to both arms and was partially relieved by a tablet of glyceryl trinitrate, 0.6 mg., placed under the tongue. All the following morning dull pain persisted in the precordium. Because of his extreme discomfort, at 11:00 A.M. (May 1) a number of exquisitely tender spots in the left pectoral muscles were infiltrated with procaine hydrochloride (0.25 per cent solution), and the chest pain ceased immediately. The response of pain to therapy is shown in Fig. 1.

During the preceding years, several acute episodes of pain in the low back, shoulder, and neck had each been promptly relieved by procaine infiltration of the trigger areas in the appropriate skeletal muscles. Because of the previous history of somatic pain and its relief by local injection therapy, the patient disregarded the possibility that the present attack of chest pain might be of cardiac origin, and insisted on continuing his regular activities.

On the following day (May 2), he drove to the country and worked in the garden. The next morning (May 3), he was awakened at 7:00 A.M. by severe substernal pain. One-half hour later, glyceryl trinitrate (0.6 mg.) was followed by appreciable diminution in pain. He remained in bed, but a heavy dull discomfort in the chest persisted during the day. At 2:00 P.M. an electrocardiogram was taken (Fig. 2,*B*). Seven hours after the onset of protracted pain, several tender spots in the left pectoral muscles were again infiltrated with procaine. This procedure secured immediate and complete relief of pain (Fig. 1).

Examination of the electrocardiogram showed evidence of myocardial damage as compared with the most recent control (Fig. 2,*A*), but owing to the long interval between these two records, the changes were considered compatible with, but not necessarily conclusive of, a recent myocardial infarct.

On May 4 and 5, the patient reported that he was "feeling fine" and insisted on going to his office. On May 5, a second electrocardiogram (Fig. 2,*C*) was taken which showed serial changes in the T waves. The blood sedimentation rate was elevated, with a total fall of 32 mm. in one hour. In view of these findings, on May 7, about a week after the initial appearance of precordial pain and four days after the onset of more severe chest and arm pain, the patient was persuaded to accept the diagnosis of acute myocardial infarction, and although he had had no further pain, to remain in bed for a period of six weeks. Later electrocardiograms (Fig. 2,*D*) confirmed the diagnosis and showed the classical changes of an anterior wall infarct.

The patient remained asymptomatic and made an uneventful recovery, although after the period of bed rest it required several weeks for him to regain his former vigor. There was no recurrence of pain following the second procaine infiltration during the ensuing two years. Follow-up electrocardiograms were normal on several occasions (Fig. 5*A*).

Second Myocardial Infarct: On May 29, 1945, the patient returned to his home at 5:30 P.M. and complained of substernal discomfort which disappeared after taking a tablet of glyceryl trinitrate (0.6 mg.). Subsequent questioning revealed that for four or five weeks previously he had not been able to lie comfortably on the left side at night because this position induced a vague discomfort in the precordium and sensation of air hunger and constriction of the chest.

On the night of May 29, the patient was awakened at midnight by a most intense substernal pain which radiated down the left arm and which was uninfluenced by repeated doses of glyceryl trinitrate (0.6 mg.) either then or later in the night (Fig. 1). Morphine sulfate (15 mg.) at 4:30

A.M. gave negligible relief, and codeine sulfate (60 mg.) at 8:00 A.M. gave no relief. At 9:15 A.M., the patient received a second dose of morphine sulfate (15 mg.) after which he became moderately comfortable for the first time since midnight. However, relief lasted for only a short while and the pain had returned to its previous intensity before noon. At this time (12:30 P.M.), twelve and one-half hours after the onset of protracted pain, two discrete areas of exquisite tenderness in the left pectoral muscles and one site in the serratus anterior muscle in the axillary region (Fig. 3) were infiltrated with a 0.25 per cent solution of procaine hydrochloride. The second injection was followed at once by the complete disappearance of pain. The restlessness and anxiety vanished simultaneously and the patient remarked that for the first time he felt as if he could take a deep breath. The blood pressure, which ordinarily was about 160/90, at this time was 120/80. The rectal temperature was 97.5° F. (Fig. 4). After the local infiltration, the patient slept most of the afternoon and had no recurrence of pain and no further analgesic medication. A diagnosis of a fresh myocardial infarct was made.

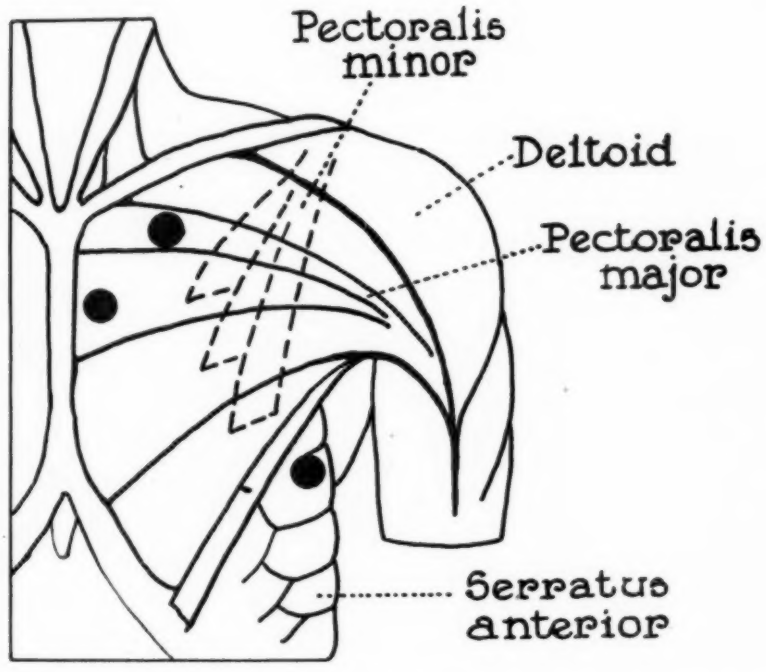

Fig. 3.—Case 1. Second infarction. Dots mark localized areas of deep hyperalgesia discovered in the precordial region following onset of cardiac pain. Procaine infiltration of trigger areas in the muscle at these two sites immediately abolished deep tenderness and also constant chest pain initiated by cardiac lesion.

The clinical course is shown in Fig. 4. At 9:00 A.M. on the following morning (May 31), the rectal temperature had risen to 99.6° F., and the blood pressure had dropped to 95/60. An electrocardiogram (Fig. 5,*B*) revealed the Q_1T_1 pattern of an anterior wall infarct. At 4:30 P.M. the blood sedimentation rate was 31 mm. at the end of one hour, and the rectal temperature was 102° Fahrenheit. The patient was hospitalized at this time. On admission he did not appear critically ill. The blood pressure was 106/70 and returned gradually to a level of 140/80 at the end of the hospital stay. The temperature returned to normal on the sixth day after the onset. The blood sedimentation rate on the twelfth day of illness had risen to 42 mm. in one hour, and was still elevated on the day of discharge. The white blood cells on the day of admission were 10,700

per c.mm. and returned to normal coincident with the disappearance of fever. Subsequent electrocardiograms (Fig. 5,*C* and *D*) confirmed the diagnosis of acute coronary thrombosis with infarction of the anterior wall.

The patient was asymptomatic during the entire hospital stay. Owing to changes in our views regarding bed rest, he was allowed out of bed in about three weeks, and went home four weeks after the onset. At the present time the patient is physically active, and has had no recurrence of pain during the intervening two years. The blood sedimentation rate in November, 1946, was 13 mm. at the end of one hour, and the electrocardiogram was normal.

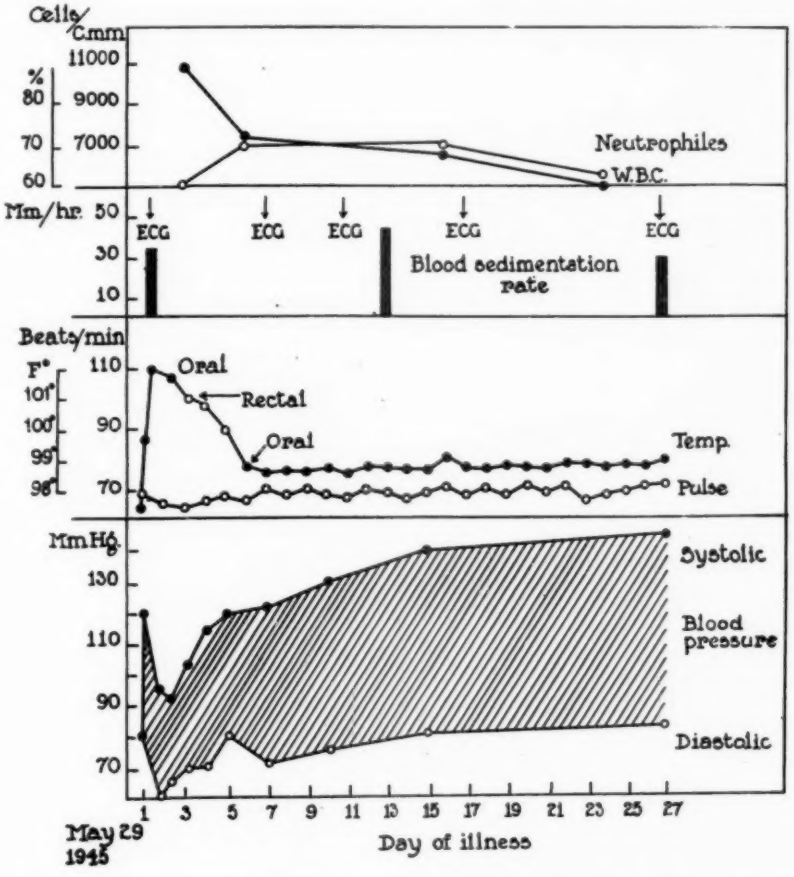

Fig. 4.—Case 1. Second infarction. Clinical course and results of laboratory tests.

Comment: The observations in this case attest the role of the somatic component in cardiac pain. Two separate myocardial infarctions occurred two years apart. The diagnosis each time was substantiated by unequivocal serial changes in the electrocardiogram and by signs of tissue necrosis. Each infarction was accompanied by protracted chest pain which was completely relieved at once by local infiltration of the appropriate areas in the pectoral muscles seven and twelve and one-half hours, respectively, after the onset of cardiac pain. The relief of pain in the first instance lasted until the next infarction, and in the

second instance, has persisted to the present time. Thus, local injection therapy obviated the need for narcotic drugs and simplified the general management of the patient. There is no evidence, however, that such therapy altered the course of the disease.

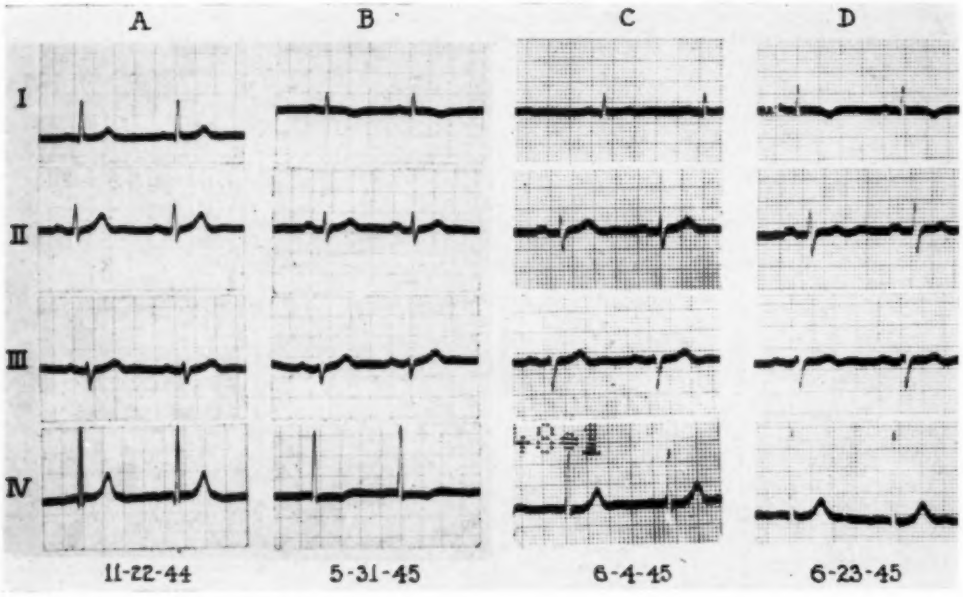

Fig. 5.—Case 1. Second infarction. Serial changes of a fresh myocardial infarct. *A*, Tracing taken one and one-half years after the first, and six months before the second infarct. Normal record. *B*, Record taken about forty hours after onset of severe chest pain, and twenty-eight hours after complete relief of pain by procaine infiltration. Note inversion of T_1 and T_4. *C* and *D*, Records taken on the sixth and twenty-sixth days of illness. Note persistence of inverted T_1, but restoration of T_4 to normal.

In the case of the first infarction, the erroneous assumption was made at first that since local block of the trigger areas in the skeletal muscles abolished pain, the pain must be of somatic origin. It is important to recognize that a visceral etiology of pain cannot be excluded by the fact that pain disappears after local block of trigger areas in somatic structures.

CASE 2. *Block by Ethyl Chloride Spray in Acute Myocardial Infarction.*—At 3:30 P.M. on Oct. 10, 1946, following an argument with a member of his family, L. Lu., a 52-year-old white male garment worker, had a sudden attack of severe precordial pain which radiated to the left side of the neck, to the left shoulder, and down the arm to the fingers. He was hospitalized at once.

On admission, physical examination revealed an acutely ill man in obvious distress. There was no dyspnea or orthopnea. The neck veins were not distended. The heart was not enlarged. There were no thrills or murmurs. The pulse and ventricular rates were 72 per minute. The blood pressure was 150/90. The lungs were clear. There was no enlargement of the liver or spleen. There was no edema. The temperature on admission was 98.6° Fahrenheit. The blood sedimentation rate was 10 mm. at the end of an hour.

Two electrocardiograms were taken one hour and two and one-half hours after admission, respectively, which showed serial changes (Fig. 6,*A* and *B*). In the first record there was depres-

sion of the S-T segments and T waves in Leads I and IV, and in the second, the configuration of these waves had returned to normal.

Because of severe, steady pain, the patient received demerol, 100 mg. every four hours, subcutaneously. When we saw the patient twenty-three hours after the onset of pain, he was still nauseated and complained of constant "squeezing and pressing" pain across the whole sternal and precordial regions and also in the left jaw, neck, and shoulder. Three circumscribed areas of exquisite tenderness to pressure were discovered in the precordial region over the second, fourth, and fifth intercostal spaces, respectively.

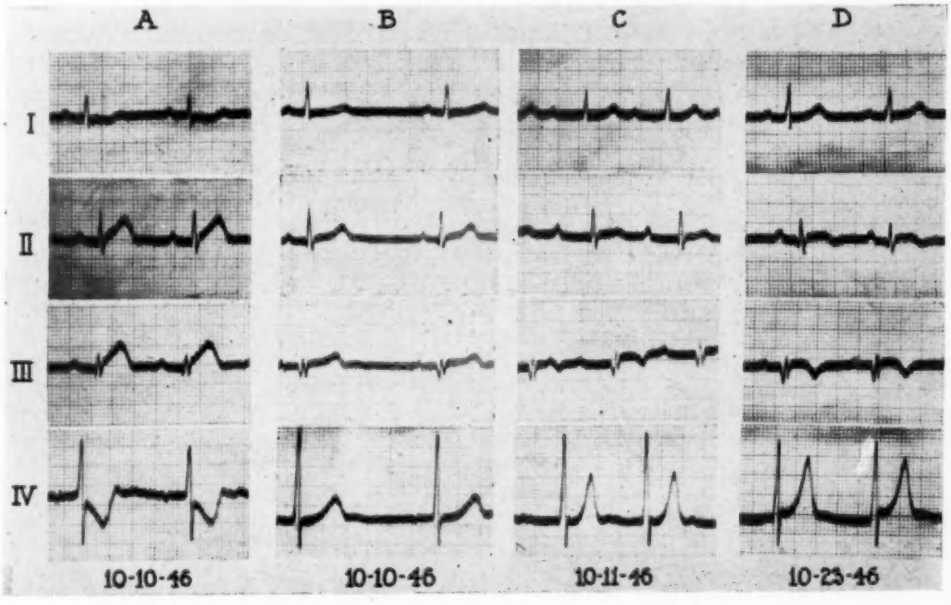

Fig. 6.—Case 2. Serial changes of a recent myocardial infarct. *A*, Electrocardiogram taken one hour after onset of precordial pain. Note depressed S-T_1 with diphasic T_1; elevated S-T_2 and S-T_3; and depressed S-T_4 with inverted T_4. *B*, Electrocardiogram taken four hours after first graph. Note appearance of Q_2 and Q_3. T waves in Leads I and IV are now elevated. *C*, Record taken twenty-three hours after onset of symptoms and immediately after ethyl chloride spray. Note Q_3T_3 pattern indicative of posterior wall infarction. Marked prolongation of A-V conduction is also present. *D*, Tracing taken thirteen days after onset of symptoms. The P-R interval has returned to normal.

Each of these tender spots was sprayed for from eighteen to twenty-five seconds with ethyl chloride, that is, until blanching or light frosting of the skin occurred. The entire procedure required approximately seven minutes. As the last of the trigger areas was thus blocked, the patient stated that the pain in the chest was completely gone. Within one-half hour, the patient had fallen asleep. Analgesic medication was stopped and no further pain occurred during the hospital stay despite the subsequent appearance of the usual signs of circulatory collapse and tissue necrosis (Fig. 7) which characterize an acute myocardial infarction.

The clinical course is shown in Fig. 7. The blood pressure fell on the second day to 90/50, and rose to 116/70 on the next day; it remained approximately at the latter level until discharge. The temperature rose to 101° F. on the third day, and returned to normal by the fifth day. The sedimentation rose to 85 mm. in one hour on the fifth day, and then gradually dropped to a level of 25 mm. on the eighteenth day. The white blood count, which was 13,000 per c.mm. on the third day, had fallen to normal by the eighth day. Further electrocardiograms revealed the changes characteristic of a posterior wall infarct as seen in the record taken on the fourteenth day (Fig. 6,*D*).

The patient was discharged from the hospital on the twenty-third day. He was observed for about six months following this infarction. He was hospitalized once because of acute infectious arthritis which responded to salicylates. He has had no recurrence of chest pain referable to the heart.

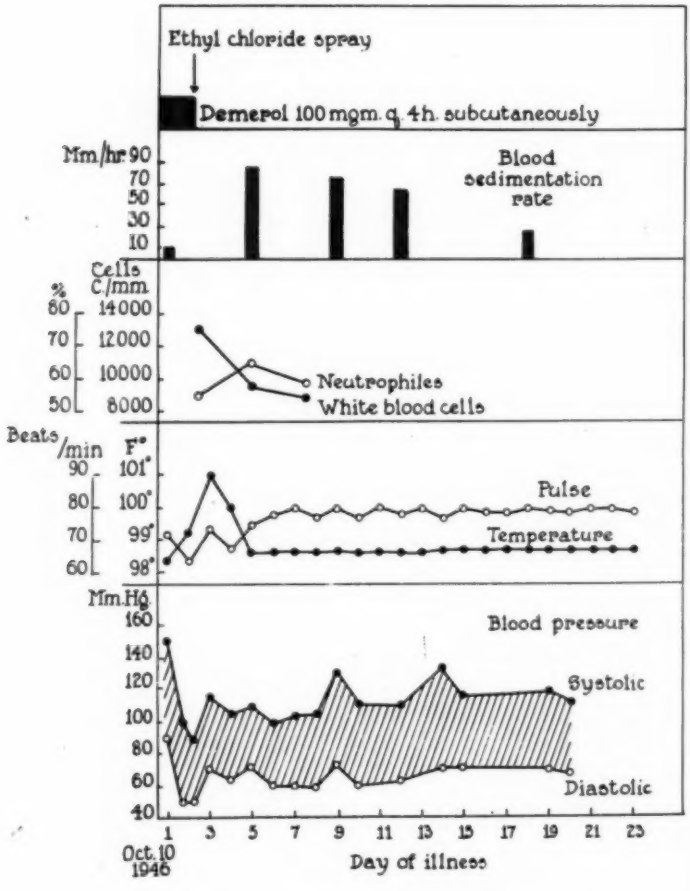

Fig. 7.—Case 2. Clinical course and results of laboratory tests. Note discontinuation of demerol after relief of pain by ethyl chloride spray.

Comment: As in the case of local infiltration of somatic trigger areas, complete and immediate relief of pain initiated by an acute myocardial infarction was obtained in this patient by ethyl chloride spray of the appropriate trigger areas in the precordium. The simplicity of the latter procedure recommends its early trial. However, in those instances in which the trigger areas are located as much as one inch or more beneath the surface of the skin, local injection may have to be substituted for ethyl chloride spray. It should be pointed out that other factors besides the depth of the trigger area, such as the chronicity of pain, may determine the choice of the procedure for local block in a particular case.

As might be expected, the abolition of pain by ethyl chloride spray did not prevent the subsequent appearance of signs of tissue necrosis or serial changes in the electrocardiogram, which establish the diagnosis of a recent infarct.

The prolongation of the P-R interval (Fig. 6,*C*), which was noted immediately after spraying with ethyl chloride, occurs so frequently as a transitory phenomenon in the course of acute myocardial infarction that in all probability it bears no relation to the use of ethyl chloride spray. An insufficient number of electrocardiograms were taken to answer this question.

The mechanism of action of ethyl chloride spray is not known.[7] It is interesting, however, that Gammon and Starr[11] found that the interrupted application of cold (4 to 10° C.) caused marked diminution of experimentally induced deep muscle pain, and attributed this effect to a poststimulatory depression of the central nervous system.

CASE 3. *Effort Angina With Postinfarction Onset.*—N. Z., a 54-year-old Italian carpenter, was first seen on June 21, 1945. For about three months he had noticed occasional mild pain in the chest on exertion. About six weeks previously, on May 7 (VE Day), he experienced a severe and protracted attack of chest pain which began after fixing the coal furnace early in the morning. Pain was oppressive across the upper part of the sternum. He put cold towels on his chest and was "very short of breath, but felt all right so long as sitting down." He was not nauseated. The "pressing" pain continued in the sternal and precordial regions all day until the doctor came at 6 or 7 P.M. and gave him "a hypo and some pills." He was told that he had had a heart attack. The patient remained in bed at home for one week. He did not take his temperature. There was no electrocardiogram or other laboratory examination.

During the six weeks following this episode of pain, effort angina was marked. On walking a short distance, pain started around the left costal margin and spread anteriorly over the entire sternum and occasionally across the front of the chest to the right side. It radiated frequently to the left interscapular region and sometimes to the left shoulder and upper arm. The pain came on sooner after effort late in the day than in the morning. There was no nocturnal pain. There was no dyspnea; the patient insisted that it was pain which stopped him from walking and not shortness of breath. There was no cough or edema.

The patient had been unable to work since the "heart attack." The course was apparently stationary; the anginal pain had become neither better nor worse during the six weeks' period.

The patient had been persuaded to give up smoking during this time, although he was always a heavy smoker of cigars. He had also markedly reduced his consumption of alcohol, which had been fairly regular, with intermittent sprees. He was taking no medication, although he had been given some tablets for pain which he preferred not to take because he said that the pain stopped anyway in about five minutes if he rested.

The previous history revealed that the patient had never been subject to "aches and pains" except for occasional mild low back pain. He had always led a very active life with little attention to his health. He had had no serious illnesses and no operations.

On physical examination (June 21), the patient appeared well nourished and muscular. The heart sounds were somewhat distant, with a soft systolic murmur at the apex. The heart did not appear enlarged. The pulse and ventricular rates were 80 per minute; the rhythm was regular. The blood pressure was 135/85. There were no signs of congestive failure. The liver edge was not palpable. The radial arteries were moderately thickened. The oscillometric readings were normal for all four extremities. The reflexes were normal and vibration sense was good in the fingers and toes. Blood Wassermann was negative. Blood sedimentation rate was 30 mm. in one hour. The electrocardiogram (Fig. 8,*A*) showed changes characteristic of an anterior wall infarct of the myocardium.

Palpation of the muscles revealed localized areas of exquisite tenderness, especially in the left pectoral muscles, but also in other muscles of the left shoulder girdle. There was no specific limitation of motion, although the patient was in general "muscle bound."

At the first visit, a group of trigger areas in the left pectoralis major muscle along the sternal border and two such tender areas located more laterally, probably in the pectoralis minor muscle, were infiltrated with procaine. A total of 20 c.c. of a 0.5 per cent solution of procaine hydrochloride (100 mg.) was used. The insertion of the needle into the myofascial structures at these sites of tenderness set off intense pain reference to the sternum, precordium, front of the shoulder, or interscapular region on the left side. The patient was always able to give a clear description of the spread of pain, which corresponded closely with the predictable reference from the trigger area in question. Tablets of glyceryl trinitrate were given him, but it may be said at this point that he never used them.

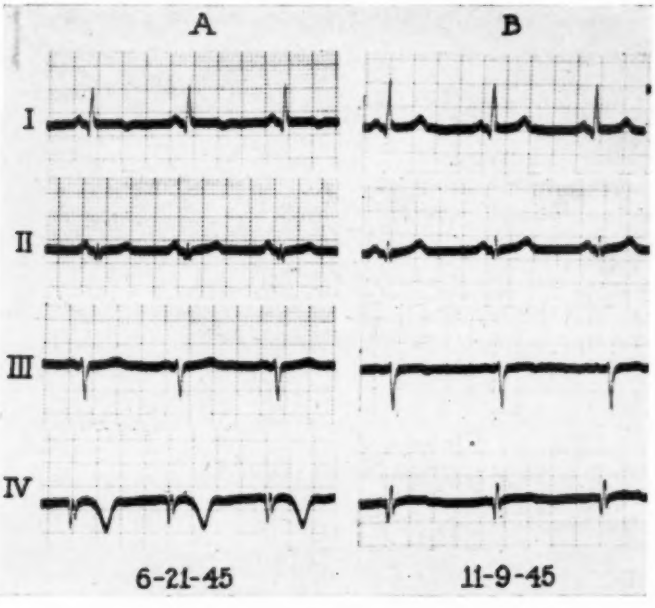

Fig. 8.—Case 3. Serial changes of myocardial infarction. *A*, Tracing taken about six weeks after acute attack of severe chest pain. Note presence of Q_1 and Q_4 and inversion of T_1 and T_4. *B*, Tracing taken five months later, after relief of effort angina by local block of somatic component. Note return of T_1 and T_4 toward normal, but persistence of Q_4.

At the second visit one week later, the patient reported striking improvement. He had had no pain after walking several blocks, except once when dull precordial pain appeared after walking five blocks; this was not severe and stopped promptly on resting. He had started to work around his house, and prior to coming to the office, made four trips from the cellar to the second floor carrying a window sash each time, without appearance of pain. At this visit, three tender areas in the precordial muscles were infiltrated, and also a larger mass of muscle in the left infraspinatus. When stimulated by the needling, trigger areas in the latter muscle repeatedly set off an intense reference of pain in the shoulder and anterior deltoid region. Twice as much of the procaine solution was used for the second as for the first treatment. No more than this amount was employed at subsequent treatments.

At the third visit, again a week later, the patient said that he could now walk any distance without pain, and that he had returned to work as a carpenter in a wartime shipbuilding plant. He had worked the three preceding nights on the night shift for nine, nine, and seven hours, respectively, without ill effects. His only complaint was that for one day he had had sharp, intermittent pain over the left scapula, apparently unrelated to effort. At this visit, trigger areas were found deep in the left internal rotator muscles of the shoulder (subscapularis and teres major),

which on infiltration set off an intense reference of pain to the region of spontaneous pain over the scapula, as well as along the inner aspect of the upper arm as far as the medial epicondyle of the elbow.

At the fourth visit one week later, the patient reported practically no pain, and he had worked four nights for nine and one-half hours each. His only complaint was of occasional low-grade interscapular pain. Trigger areas were again found in the internal rotator muscles of the left shoulder, and on infiltration the pain reference matched the distribution of spontaneous pain. At this time, little tenderness could be elicited by palpation of the left pectoral muscles in the previous areas of deep hyperalgesia, and on needling the slightly tender spots in the precordium, the pain perceived was negligible and was felt only locally at the site of needling.

At the fifth visit on July 27, after an interval this time of two weeks, the patient said that he had worked seven nights during the first week and six nights during the second, without pain. The work was fairly heavy but he said that he "took it easy and didn't hurry." He complained however of "a light choking feeling in the throat" which began after walking eight blocks with a box of heavy tools on his back and which had persisted off and on ever since. This disagreeable sensation was traced to trigger areas present in the uppermost sections of the pectoralis major muscles on both sides close to the sternum and the clavicles, which set off a reference of pain to the sternum at this level and to the upper part of the trachea. Trigger areas located in the inferior end of the medial heads of the sternomastoid muscles were also infiltrated and induced an upward reference of pain over the sides of the neck.

Subsequently, the patient was seen once a month for five months. He continued to work regularly except when he was "laid off" for a couple of weeks after closing of the war plant on September 10. During this five-month period, he had no real chest pain, in spite of strenuous physical activity which included lifting and carrying lumber. A good part of his carpentry was done outdoors on the exterior of the ships, even in cold and stormy weather. Minor complaints of shifting low-grade pain in the left lower lumbar, left shoulder, right pectoral, and epigastric regions were relieved in each instance by local procaine infiltration of trigger areas in the appropriate muscles, the pain reference from which reproduced the spontaneous pain described. The monthly blood pressure readings were as follows: 142/88, 120/60, 110/60, 110/70, and 150/95. The soft systolic murmur at the apex disappeared. Signs of congestive failure were absent. On November 9, the blood sedimentation rate was 20 mm. in one hour, and the electrocardiogram (Fig. 8,*B*) had returned essentially to normal except for a deep Q_4. The patient had gained about ten pounds and had not resumed smoking.

The last observation of the patient was on Dec. 6, 1946. At this time, activity was slightly limited in that if he worked hard and at the same time hurried, he occasionally felt a tightness across the upper part of the sternum or in the epigastrium which disappeared promptly on resting. However, this did not bother him enough to keep him from working and did not seem to warrant. further treatment.

Comment: In this case, severe effort angina precipitated by an acute myocardial infarct caused total disability from work for a period of six weeks, and showed no tendency toward spontaneous improvement even though the patient had given up smoking and drinking. After this "control" period, the first local block of the most conspicuous trigger areas in the precordial muscles afforded about 90 per cent relief of the anginal pain. Within a few days after the second local infiltration one week later, the patient returned to his previous heavy work in wartime ship construction. During the ensuing five months of observation he continued at his job without loss of time and with freedom from anginal pain, even though he worked outdoors during inclement weather often seven nights per week.

DISCUSSION

Experimentation in animals and human subjects has led to controversy as to whether local anesthetization of the somatic tissues in the area where pain is perceived can block the referred pain induced by direct stimulation of a viscus. A complete analysis of this subject would be out of place in this report since the problem has been recently reviewed.[12] However, it may be pertinent to note that the discrepancies in the literature probably arise at least in part from differences in the character of the stimulus employed, in the nature of the tissue (superficial or deep) infiltrated with procaine, and in the technical difficulties in the way of complete anesthetization of the deeper structures in the area of visceral pain reference. After consideration of such variables and on the basis of their own experiments, Wolff and Hardy[12] conclude: "When pain results from the persistence of primary visceral or other deep noxious stimulation and is associated with [somatic] hyperalgesia, its intensity may be modified by superficial and deep procaine infiltration in the hyperalgesic zones."

Our data suggest that the somatic trigger mechanisms which apparently mediate referred cardiac pain are usually located within the skeletal muscles, although they may reside also in the skin. In the latter instance, cutaneous as well as deep hyperalgesia is present, and a reference of pain may often be elicited by mechanical stimulation of the skin itself. One would expect surface anesthetization to reduce pain only when hyperalgesia of the skin is present, since it has been found[13] that the effect of procaine infiltrated at the site of hyperalgesia and referred pain (induced by tooth stimulation) is the more dramatic the greater the hyperalgesia and headache previously produced. We have observed, however, that ethyl chloride spray may be effective in relieving referred pain even when no hyperalgesia of the skin is detectable. Although the mechanism of action of this agent in blocking somatic trigger mechanisms is not yet established, the superficial nature of its effects[7] for the technique employed suggests the possible importance of tactile and other stimuli from the relatively normal skin in the maintenance of the pain cycle. It has been inferred that reinforcement of the effects of noxious stimuli by nonnoxious stimuli takes place within the association areas of the cerebral cortex.[12]

Our observations indicate further that the noxious stimuli from the heart, continuing after acute myocardial infarction, are of such a nature that the pain cycle initiated by this event can usually be blocked at the somatic component. Why this is so can readily be understood in the case of the *constant* pain which may continue for hours or days after such brief trauma to the heart. The conditions may be regarded as analagous to those which exist in joint sprain when pain is immediately and permanently relieved by temporarily blocking the trigger mechanisms established in the periarticular structures, in spite of the persistence of gross signs of trauma.[7] One may assume that in the postinfarction cardiac pain syndromes, the initial insult to the heart leads to the rapid development of somatic trigger areas within the so-called "reference zone" of the visceral lesion. Soon after the activation of the somatic trigger mechanism, the noxious impulses from the primary source in the heart cease spontaneously, and the con-

tinuation of pain then depends on an autogenic cycle of nerve impulses maintained by the secondary sources in the somatic structures. Blocking the somatic component may be expected permanently to abolish pain when the soma-sensorium pain cycle has become self-sustaining without further dependence on afferent impulses from the heart (Fig. 9, Stage III).

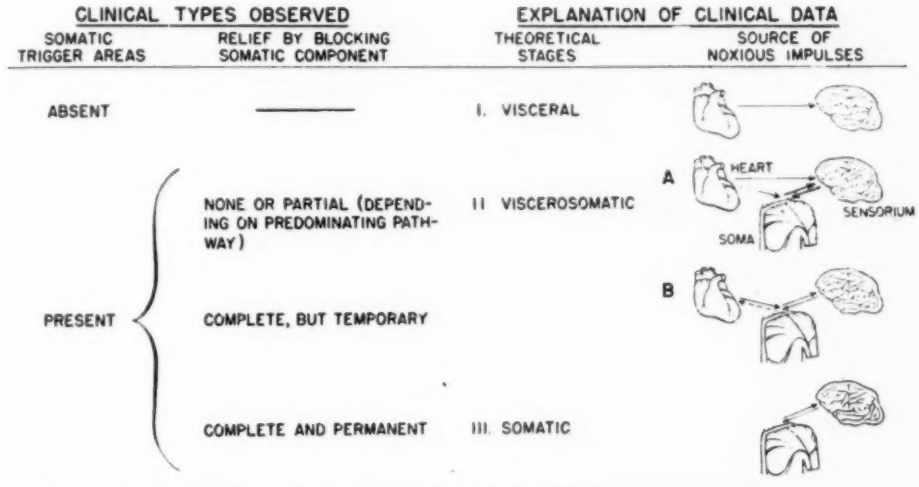

Fig. 9.—Interpretation of results of local block of somatic component in cardiac pain. Stage I represents direct stimulation of sensorium by high intensity stimuli from heart, as in onset of coronary thrombosis or insufficiency. In many patients process ends here without progression to Stages II and III. Stage II represents continuation of process in heart with development of somatic trigger areas continually reactivated by noxious impulses from the heart, as in effort angina. The dotted arrow *B* suggests that noxious impulses may also travel from somatic trigger areas back to the heart. Stage III represents termination of process responsible for noxious impulses from heart. Somatic trigger mechanisms are now independent and are the sole source of impulses to maintain the pain cycle, as in protracted pain after myocardial infarction.

In the case of the *intermittent* pain (effort angina) precipitated by acute myocardial infarction, it is somewhat harder to understand why blocking the somatic component modifies pain for any length of time, since it is clear that a primary source of noxious impulses is still present in the heart. One would anticipate that, under such circumstances, constant reactivation of somatic trigger mechanisms would occur as the result of the intermittent barrage of fresh impulses from the heart, and that, therefore, block of the secondary sources would produce only temporary or negligible benefit.

One explanation of the good therapeutic results actually observed in this group of cases is based on the concept that spatial summation of cardiac and somatic impulses occurs in the central nervous system.[14] Thus, it is conceivable that when the stimuli initiated in the heart are subthreshold, the sensorium does not register pain unless they are reinforced by stimuli from somatic trigger areas (Fig. 9, Stage II,*A*). One may postulate further that these subthreshold stimuli from the heart are no longer capable of activating new trigger areas after those initiated by high intensity stimuli at the time of infarction have been removed by local block. That pain impulses may at times travel directly from the heart to

the brain without mediation of somatic structures is suggested by our failure to demonstrate trigger areas in the precordium in some patients with acute myocardial infarction or effort angina (Fig. 9, Stage I).

Another explanation for the protracted relief of postinfarction effort angina by local block therapy is based on the possibility that the somatic trigger mechanisms contribute to the perpetuation of the primary source of pain (Fig. 9, Stage II,*B*). Although our data provide no evidence that noxious impulses from somatic trigger areas may modify conditions in the heart, the inference that such reflex effects may occur receives support from the work of several investigators. Lindgren[15] showed in acute experiments that anginal pain in subjects with coronary artery disease was reduced or abolished during local anesthetization of precordial structures, as measured by changes in anoxia and exercise tolerance tests; this effect was attributed to improvement in the coronary circulation during local block of somatic impulses. Furthermore, it has been shown that reflex vasoconstriction in localized areas of another visceral system, namely, the brain or spinal cord, may accompany activity of somatic trigger mechanisms, and that localized vasodilatation in the central nervous system may follow local block of the appropriate somatic trigger areas.[16,17] If comparable relationships apply to the heart, local block of the somatic trigger areas concerned in the reference of cardiac pain would result in release of coronary vasospasm and possibly, therefore, in removal of the primary source of noxious impulses in the heart.

The unsatisfactory response to local block therapy in the group of patients with effort angina due to progressive coronary insufficiency indicates that such intermittent work-ischemia of the heart muscle provides conditions unlike those which exist in postinfarction effort angina. Two possibilities present themselves to explain the relatively poor therapeutic result in angina of gradual onset. It may be that the fresh impulses initiated in the heart with each attack of pain are of an intensity and duration adequate for the continual reactivation of somatic trigger areas (Fig. 9, Stage II,*B*). Or a preponderance of these fresh impulses may travel directly to the sensorium, so that spatial summation of cardiac and somatic impulses is not essential for the perception of pain (Fig. 9, Stage II,*A*). In either instance, local block of the somatic trigger areas would be expected to afford negligible or temporary relief of anginal pain.

Our interpretation of the results of local block therapy as presented in the foregoing and as shown schematically in Fig. 9, is in harmony with the categories of referred pain recently formulated by Wolff and Hardy.[12]

It is to be hoped that theoretical considerations regarding neurophysiologic mechanisms will not obscure the clinical value of local block procedures for the symptomatic relief of cardiac pain. The crucial nature of our observations in the subjects with continuing pain after acute myocardial infarction leaves no room for doubt that under suitable conditions cardiac pain may be abolished by local block of the somatic component. Furthermore, the importance of eliminating all possible factors which may induce reflex spasm of collateral coronary arteries is emphasized by experiments which show that interruption of the reflex arc by ablation of the cardiosensory pathways appreciably lowers the mortality

rate following ligation of the coronary arteries in dogs.[18] These findings, together with the observations of Lindgren,[15] undermine the concept occasionally encountered that pain, especially anginal pain, is a protective mechanism to limit the load placed on the myocardium with an inadequate coronary circulation.

SUMMARY AND CONCLUSIONS

1. Observations were made in thirty-one subjects with chest pain due to inadequacy of the coronary circulation, who presented trigger areas in the muscles of the precordium.

2. Local block of the somatic structures concerned in the reference of cardiac pain was carried out either by infiltration of the appropriate trigger areas with a solution of procaine hydrochloride (0.25 to 0.5 per cent in physiologic saline), or by spraying the skin overlying these trigger areas with ethyl chloride.

3. The cardiac pain syndromes which responded to local block of the somatic component were those precipitated by an acute myocardial infarct. This was true for the constant chest pain which failed to subside after infarction (four subjects), and for effort angina which first appeared shortly after infarction (twelve subjects).

4. Unsatisfactory results were obtained by local block in effort angina (fifteen subjects) which either antedated the first infarct or was not accompanied by a known myocardial infarct.

5. The difference in the therapeutic response observed for the two general modes of onset of effort angina was not attributable to differences in age or sex distribution, duration of anginal pain, or incidence of hypertension.

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COMBINED HEPARIN-DICUMAROL THERAPY OF MYOCARDIAL INFARCTION

A Clinical and Pathologic Study

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UNTIL recently, anticoagulants have been used largely in the treatment of venous thrombosis and peripheral arterial occlusion. However, both experimental and clinical evidence has accumulated to indicate that anticoagulants may also have their place in the treatment of coronary thrombosis and myocardial infarction. Solandt and Best[1] demonstrated that heparin could prevent coronary thrombosis experimentally induced in animals. Solandt and associates[2] also showed experimentally that heparin prevented the development of mural thrombosis over an area of injured cardiac muscle. Dale and Jaques[3] have shown that dicumarol prevented venous thrombosis in experimental animals. Recently, Ogura and associates[4] reported that, following myocardial infarction, there was evidence of increased coagulability of the blood.

The use of anticoagulants for the treatment of myocardial infarction has become of especial interest to clinicians in the hope that certain complications could be averted. The frequent occurrence of mural thrombosis overlying a myocardial infarct and the subsequent occurrence of severe and often fatal emboli have been reported by a number of authors.[5-10] Recently, Nay and Barnes[11] have emphasized the high incidence of embolism occurring during the immediate convalescence from acute myocardial infarction. The work of Peters and co-workers,[12] Nichol and Page,[13] and Wright[14] seems to indicate that dicumarol is of definite value in preventing emboli following myocardial infarction.

Loewe and Hirsch[15] have shown that heparin will prevent occlusion of collateral veins after traumatic thrombosis of a larger vein. There is a latent period of twenty-four to seventy-two hours before dicumarol becomes effective. During this period, the clot in the coronary artery may extend in a retrograde direction, thus enlarging the area of infarction; therefore, it was thought advisable to administer both heparin and dicumarol initially. When the prothrombin concentration in the blood was reduced to the desired level, heparin* was discontinued.

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*The heparin for this study was furnished through the courtesy of the Abbott Laboratories, North Chicago, Ill.

In order to evaluate combined heparin-dicumarol therapy, anticoagulant treatment was administered to alternate patients with myocardial infarction; in all other respects, the therapy was identical. This study was begun independently in April, 1946, at the Cincinnati General Hospital and has continued since February, 1947, in collaboration with the "Committee on the Use of Anticoagulants in the Treatment of Coronary Thrombosis With Myocardial Infarction," of the American Heart Association.

PROCEDURE

Treatment was begun as soon as a definite diagnosis of myocardial infarction could be established, employing the usual clinical, laboratory, and electrocardiographic criteria. All patients were treated within twenty-four hours of the onset of symptoms, except two, who were treated on the second and third day, respectively. Anticoagulant therapy was not begun until an initial prothrombin and clotting time had been determined, using the capillary tube method. The usual initial dose of dicumarol consisted of 200 mg. orally, unless the prothrombin time was prolonged or the patient in severe shock. Simultaneously, 300 mg. of heparin were added to a liter of 5 per cent glucose in water and a continuous intravenous drip was started at the rate of 20 drops per minute. Subsequently, the rate of the drip was regulated in accordance with measurements of the clotting time by the capillary tube method. The clotting time was determined at four-hour intervals, except between 12 midnight and 8 A.M. An attempt was made to maintain the clotting time between 8 to 10 minutes and the rate of the drip was increased or decreased accordingly. The required rate usually averaged between 20 and 25 drops per minute; an occasional patient, however, needed as much as 35 drops per minute. Although the capillary method was only relatively accurate, nevertheless, it seemed that this method was preferable to methods requiring repeated venepunctures.

The prothrombin time was determined approximately twenty-four hours after the initial dose of dicumarol, and daily thereafter until the discontinuance of dicumarol on the twenty-first day. The prothrombin was determined by the method of Quick, using freshly drawn blood and a control plasma for each determination. The results were reported not only as "prothrombin times," but as percentages of normal concentration, using Quick's curve and correcting for each lot of thromboplastin* which was freshly prepared each day.

Heparin was discontinued when the prothrombin concentration fell to 20 to 30 per cent of normal concentration,[16] which usually occurred between twenty-four and thirty-six hours after the first dose of dicumarol. The average patient required between 300 to 400 mg. of heparin during this period. Subsequent dosage of dicumarol was administered only after the daily estimation of prothrombin. The importance of accurate laboratory determinations of the prothrombin concentration should be emphasized.[17] An attempt was made to maintain the prothrombin concentration between 20 per cent and 30 per cent of normal. The daily dosage varied from 0 to 250 milligrams. When the pro-

*Difco Laboratories, Detroit, Mich.

thrombin concentration was above 30 per cent of normal, 100 to 200 mg. of dicumarol was administered; if below 20 per cent of normal, none was given. It should be understood that the dosage of dicumarol varied greatly from patient to patient, and that there was no true "standard dosage." The total dosage of our twenty-five treated patients during the twenty-one-day period of therapy ranged from 800 to 2,200 mg. of dicumarol. A period of twenty-one days was selected for therapy, since previous work had shown that by the twenty-first day after myocardial infarction, the coagulation of the blood was no longer accelerated.[4]

RESULTS

The results are summarized in Tables I, II, and III. All patients tolerated the intravenous drip well. It was noted in many instances that the intensity of the pain and its duration seemed markedly reduced by the intravenous administration of heparin in glucose. No patient receiving heparin therapy suffered pain of longer duration than sixty hours after the institution of treatment; in fact, many were immediately relieved of pain. Since no control observations using glucose alone were carried out, and since the psychologic factors associated with intravenous therapy may have played a role, further observations are necessary before conclusions concerning relief of pain by heparin, per se, can be drawn.

Fifty cases of myocardial infarction have been observed: twenty-five "treated" and twenty-five "untreated" patients. For purpose of brevity, "treated patients" indicates those receiving anticoagulant therapy, and "untreated" those who did not. Five of the treated patients and three of the controls were observed in private hospitals; the others were patients in the Cincinnati General Hospital. It should be emphasized that in the Cincinnati General Hospital private nursing care was not available. The patients were given routine care on a large medical ward. Three of the treated cases and eight of the untreated cases have died. All of the treated cases who died were found to have massive myocardial infarction at necropsy. None showed mural thrombosis or emboli. The case histories and pathologic findings of the three fatal cases who received anticoagulant therapy are appended.

CASE 9.—The patient was a 50-year-old white man. The present illness began on June 10, 1946, with vicelike pain in the chest accompanied by weakness, fainting, and perspiration. Six hours later, when admitted to the ward, the patient appeared acutely ill and in profound shock. The blood pressure when obtainable was 110/80, the pulse was extremely irregular, the rate varying between 32 and 40 per minute. The heart sounds were heard with difficulty. The initial diagnosis was acute myocardial infarction. An electrocardiogram showed complete A-V block with a slow idioventricular rate and classical signs of posterior infarction. Six hours after admission the patient had a convulsive seizure which was followed by syncope. This was thought to be a Stokes-Adams attack.

Heparin, 300 mg., was administered intravenously. After determination of the initial prothrombin time (12.5 seconds), the patient was given 200 mg. of dicumarol. Twenty-four hours later, when the prothrombin time had increased to twenty seconds, heparin was discontinued. An additional 100 mg. of dicumarol was given, the total dosage in forty-eight hours being 300 milligrams. On the second hospital day, two additional attacks of Stokes-Adams syncope occurred and the patient excreted only 100 c.c. urine in twenty-four hours. During this period, the heart sounds were barely audible and the pulse was frequently imperceptible. On the third

TABLE I. COMBINED HEPARIN-DICUMAROL THERAPY IN ACUTE MYOCARDIAL INFARCTION

	PATIENTS RECEIVING ANTICOAGULANTS	PATIENTS NOT RECEIVING ANTICOAGULANTS
Number	25	25
Age (mean*)	56.6	58.6
Sex		
Male	88%	72%
Female	12%	28%
Race		
White	92%	84%
Negro	8%	16%
Previous hypertension	60%	44%
Previous heart disease	44%	44%
Previous coronary occlusion	16%	28%
Cardiac enlargement	48%	44%
Diabetes	20%	0
Treatment		
Dicumarol (mg.) mean dosage†	1,421	—
Heparin (mg.) modal	300	—
Digitalis	12%	40%
Complications		
Emboli	4%	24%
Congestive failure	16%	40%
Shock	12%	12%
Hemorrhage	12%	—
Duration of pain after admission (average)‡	18.6 hr.	48 hr.
Died	12%	32%

*Mean Treated 56.6 ± 1.56 σ = 11.55 years
Mean Control 58.6 ± 1.47 10.91 years
Diff. = 2 years
P_e diff. = ± 2.14 years
Diff. = 2.0 ± 2.14 years, which is not statistically significant. Therefore both groups are identical as to mean age.

†Calculations based on patients receiving entire course of therapy.

‡Calculations based on patients having severe pain after admission.

hospital day the prothrombin time was 58 seconds, with a control of 14 seconds. By afternoon, two hours before death, it had risen to 120 seconds. One hundred twenty milligrams of vitamin K1 (menadione) were administered without apparent response. The urea nitrogen a few hours before death was 78 mg. per cent. The patient died fifty-two hours after admission.

Autopsy.—The heart weighed 430 grams. The coronary ostia were patent. The trunk and branches of both coronary arteries were tortuous and sclerotic. The right coronary artery was occluded by a thrombus about 4 cm. from orifice of the vessel. The clot measured 1 cm. in length. The epicardium was smooth and contained two pin-point hemorrhages near the apex.

Examination of the myocardium revealed a large area of friable yellow tissue involving the entire length of the posterior portion of the intraventricular septum. The endocardium was intact. The remainder of the myocardium was somewhat brownish in color. The aorta was sclerotic, with numerous dull yellow plaques on the intima. No evidence of gross or microscopic hemorrhage was noted in any organ at autopsy. The brain likewise showed no evidence of hemorrhage.

The pathologic diagnoses were: (1) Far-advanced arteriosclerosis of the coronary arteries with recent occlusion of the right coronary artery by rupture of an atheromatous plaque and subsequent thrombosis. (2) Acute progressive myocardial infarction of the posterior portion of the interventricular septum. (3) Marked chronic passive congestion of the lungs, spleen, and liver with central necrosis in the liver. (4) Possible toxic nephrosis (eighteen hours post mortem). (5) Marked focal fibrosis of the alveolar walls of the lung, possibly from an old pneumonia. Marked chronic passive congestion of the lungs.

CASE 13.—This patient, an 80-year-old white woman, was admitted to the Cincinnati General Hospital on Nov. 14, 1946, and died the next day. The present illness began on the day of admission with a feeling of constriction in the chest and precordial pain with radiation to the right shoulder and back. Her family noticed marked cyanosis of the lips. Two weeks before admission facial weakness and weakness of the right hand developed and persisted to the present admission. A midthigh amputation of the right leg had been performed three years previously in another hospital for diabetic gangrene. There had been no attempt to control the diabetes during this three-year interval.

After the determination of the prothrombin time (12 seconds), 100 mg. of dicumarol was given by mouth and continuous intravenous administration of heparin was begun. During a twelve-hour period the patient received 200 mg. of heparin. It was noted that the pain, which had been intense on admission, diminished after the heparin was begun and no narcotics were given. One and one-half hours before death, the clotting time was reported as 7.5 minutes (Lee and White). The urine showed 1 plus sugar and 1 plus albumin. While speaking to the nurse, the patient suddenly died twelve hours after admission.

Autopsy: When the breast plate was removed, about 200 c.c. of dark red, clear fluid was found to be present in the left pleural cavity, and about 100 c.c. in the right pleural cavity. A few thin pleural adhesions were present. The blood flowed readily on cutting through the various tissues, and appeared to be more fluid than usual. The pericardial sac measured 15 cm. in its greatest transverse diameter in a chest that measured 30 cm. in its greatest diameter. On incision, dark red blood escaped from the pericardium, as if under pressure. About 150 c.c. of fluid blood were present in the pericardial cavity. In addition, a soft, "current jelly" clot of blood, measuring about 6 mm. in diameter, surrounded the entire heart. It was estimated that between 250 and 300 c.c. of blood were present in the pericardial cavity. The pericardium was lined by smooth and glistening membrane. The thoracic organs were in their normal positions and relationships.

The heart weighed 425 grams. On the epicardial surface of the posterolateral aspect of the left ventricle, about 3 cm. above the apex, there was an erosion measuring 1 cm. in length and 2 mm. in width. This erosion was ragged in appearance. Higher up on the posterolateral aspect of the left ventricle, just below the atrioventricular margin, dark red mottling of the epicardium extended over a diameter of about 3 cm., but there was no erosion in this area. The left circumflex coronary artery was moderately sclerotic but widely patent up to a point about 4 cm. from its origin. At this point, the artery became markedly narrowed for about 2 cm. of its length, and then its lumen again widened out. In the narrowed portion of this artery, where the lumen measured about 2 mm. in diameter, there was found a pink, soft, irregular mass elevated about 1 mm. above the intima. This pink mass occupied about 1 cm. of the length of the artery. On making sagittal sections through the left ventricle, a diffuse, irregular dark mottling of the pink myocardium was observed. This mottling was particularly noticeable between the erosion previously mentioned, at the lower aspect of the ventricle, and the hemorrhagic area in the epicardium previously noted. This mottling appeared to extend in a few places as far as the endocardium. No communication was present between the ragged erosion and the chamber of the left ventricle

TABLE II. PATIENTS WITH MYOCARDIAL INFARCTION TREATED WITH HEPARIN-DICUMAROL THERAPY

NO.	AGE	SEX	RACE	PREV. HYPERTENSION	PREV. HEART DIS.	PREV. COR. OCCL.	CARD. ENLARG.	OTHER DISEASES	TREATMENT			COMPLICATIONS				ECG		DURATION OF PAIN AFTER ADMISSION	DIED	COMMENTS
									DICUMAROL (MG.)	HEPARIN (MG.)	DIGITALIS	PULMONARY EMBOLI	CONGEST. FAIL.	SHOCK	GROSS HEMORRHAGE	ANT.	POST.			
1	59	F	W	+	+	0	+	0	800	300	0	0	0	0	0	+	0	None	0	Doing well 10 mo. after discharge
2	49	M	W	+	0	0	+	0	1100	300	0	0	0	0	0	+	0	48 hr.	0	1st admission
3	49	M	W	+	+	+	+	0	1100	300	0	0	0	0	0	0	+	24 hr.	0	2nd admission, 5 mo. later
4	42	M	W	+	0	0	0	0	1025	300	0	0	0	0	0	+	0	6 hr.	0	Symptom-free, working 4 mo. later
5	47	M	W	0	0	0	0	0	1050	200	0	0	0	0	0	+	0	60 hr.	0	Admitted to private hospital 2 mo. after discharge with second attack
6	45	M	C	+	0	0	0	0	1450	700	0	0	0	0	0	+	0	18 hr.	0	
7	57	M	W	+	0	0	+	0	1575	900	0	0	0	0	0	+	0	18 hr.	0	Angina 27th day of illness; doing well
8	47	M	W	0	0	0	0	Diabetes	1250	300	+	0	+	0	0	+	0	7 hr.	0	Congestive failure 29 days after admission; insulin; doing well
9	50	M	W	0	0	0	+	0	300	300	0	0	+	+	0	0	+	24 hr.	+	Died 48 hr. after admission; post mortem, see protocol
10	40	M	W	0	+	0	0	0	800	300	0	+	0	0	0	+	0	48 hr.	0	5th day patient had trans. facial hemiplegia and aphasia which disappeared after 24 hr.
11	62	M	W	0	0	0	0	Perirectal ulcers	1200	300	0	0	0	0	0	+	0	24 hr.	0	
12	55	M	W	+	0	0	0	Asymptomatic syphilis	1500	300	0	0	0	0	0	0	+	6 hr.	0	Doing well on antisyphilitic therapy
13	80	F	W	+	+	0	+	Diabetes	100	200	0	0	0	0	+	0	+	None	+	Death—18 hours; autopsy: incomplete rupture of ventricle
14	68	M	W	0	+	+	+	0	800	600	+	0	+	0	0	+	0	None	0	Died 2 mo. after discharge of congestive failure, pulmonary edema

15	48	M	W	+	0	0	0	0	800	300	0	0	0	0	0	+	0	6 hr.	0	Doing well; asymptomatic 3 mo. after discharge
16	64	M	C	+	+	0	+	Diabetes polycythemia	1900	600	0	0	0	0	0	0	+	6 hr.	0	Doing well; asymptomatic 2 mo. after discharge
17	72	M	W	0	+	0	0	0	2000	300	0	0	0	+	0	0	+	2 hr.	0	Occurred 14th day after spinal fusion operation; doing well
18	67	M	W	0	0	0	0	0	2000	400	0	0	0	0	0	+	0	None	0	Doing well; no symptoms 2 mo. after discharge
19	33	M	W	+	+	0	+	0	1600	400	0	0	0	0	0	+	0	12 hr.	+	Death—15th day; autopsy: large anterior and septal infarct, coronary occlusion, no mural thrombosis or emboli
20	62	M	W	0	0	0	0	0	1350	300	0	0	0	0	+	+	0	6 hr.	0	Developed gross hematuria when prothrombin time fell to 13% of normal; good response with 60 mg. menadione, feeling fine 2 weeks after discharge
21	71	M	W	0	+	+	0	Gout	1550	600	0	0	0	0	+	+	0	None	0	Doing well 6 weeks after discharge; developed tarry stool when prothrombin time 17% normal; recovered, no menadione
22	56	M	W	+	+	0	+	0	2200	300	0	0	0	0	0	+	0	12 hr.	0	Patient had attack of severe percordial pain 10 days before admission; second attack of pain on day of admission
23	61	F	W	+	+	+	+	Diabetes	1750	600	0	0	0	0	0	Ant. lat. sept. involv.	0	None	0	Patient had acute coronary occlusion 3 mo. before present attack; received dicumarol for previous attack in another hospital; is to be kept on dicumarol after discharge
24	50	M	W	+	0	0	0	0	2200	300	0	0	0	0	0	0	+	14 hr.	0	
25	74	M	W	+	0	0	+	Diabetes	1100	400	+	0	+	+	0	0	+	12 hr.	0	Patient confused and disorientated on admission; evidence of diabetic acidosis as well as coronary thrombosis; insulin required throughout

TABLE III. CONTROL SERIES OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

NO.	AGE	SEX	RACE	PREV. HYPER-TEN-SION	PREV. HT. DIS.	PREV. COR. OCCL.	CARD. EN-LARG.	DIGI-TALIS	OTHER DISEASES	COMPLICATIONS			ECG		DURATION OF PAIN AFTER ADMISSION	DIED	COMMENTS
										PUL-MONARY EMBOLI	CONGEST. FAIL-URE	SHOCK	ANT.	POST.			
1	58	F	C	+	+	0	+	+	0	0	+	0	+	0	120 hr.	0	
2	80	F	W	+	+	+	+	0	0	0	0	0	B.B.B.	+	120 hr.	0	
3	75	M	W	0	0	0	+	0	0	0	0	+	0	+	Dull entire period	+	Died 18 hr. after admission
4	59	F	W	+	+	0	+	+	Pneumonia 5 days after admission	0	+	0	0	+	None	0	
5	69	M	W	+	0	+	0	+	0	+	+	0	+	+	None	+	Acute pulmonary edema and auricular fibrillation; died 19 days after admission
6	49	M	W	+	0	0	0	0	0	0	0	0	0	+	Some dull 240 hr.	0	
7	69	M	W	0	+	0	0	0	Cholecystectomy 1946	0	0	+	+	0	24 hr.	+	Died 3 days after admission
8	51	M	W	0	0	0	0	0	0	0	0	0	0	+	12 hr.	0	Recurrence 2 weeks after discharge; treated at home; angina on effort
9	41	M	C	+	+	0	+	+	Pneumonia or congestion?	0	+	0	0	+	Dull 240 hr.	0	
10	46	M	W	0	0	0	0	+	0	0	+	0	+	0	24 hr.	0	
11	66	F	W	+	0	0	0	0	Pneumonia?	+	0	0	0	+	None	+	Died 8 days after admission; cause of death, probable pulmonary infarct; no autopsy
12	79	F	C	0	+	0	+	+	0	+	+	0	0	+	None	+	Died 8 days after admission; autopsy: septal infarct with pulmonary emboli
13	55	M	W	0	0	+	0	0	0	0	0	0	0	+	24 hr.	0	In 2 mo. ago, treated at that time with anticoagulants

14	59	M	W	0	0	+	0	0	0	0	0	0	0	+	48 hr.	0	
15	50	M	W	0	+	+	+	+	0	0	+	0	+	0	72 hr.	0	Persistent failure; no response to xanthines, mecurials
16	67	F	W	0	0	0	0	0	0	0	0	0	+	0	48 hr.	0	Doing well 2 mo. after discharge
17	36	M	W	+	+	0	+	+	0	0	+	0	+	0	48 hr.	+	Persistent dyspnea throughout illness; died suddenly 28th day of illness; no autopsy
18	52	M	W	0	0	0	0	0	0	0	0	0	+	+	Mild 48 hr.	+	Died 10th day after admission; autopsy: old anterior, recent posterior infarct; mural thrombosis
19	53	M	C	0	0	0	0	0	Cholecystitis—3 attacks last 10 yr.	+	0	0	+	0	Mild 48 hr.	0	Stormy course—2 pulmonary emboli; prolonged convalescence
20	49	M	W	0	+	+	+	0	0	0	0	0	+	0	None	0	Third admission in one year; treated twice; used as control 3rd admission
21	68	M	W	+	0	0	0	0	0	0	0	0	+	0	None	0	Doing well, no complaints 2 months after discharge
22	70	M	W	0	0	+	0	+	Peripheral vascular sclerosis	+	+	0	+	+	None	0	Patient entered with diagnosis of "pneumonia." ECG showed recent postr. infarct; while in hospital, developed anterior infarct; "pneumonia" was probably pulmonary infarct
23	57	F	W	+	+	0	0	0	0	0	0	0	+	0	None	0	Persistent angina 2nd week after admission
24	54	M	W	+	+	0	+	+	0	0	+	0	+	0	48 hr.	0	
25	74	M	W	?	?	?	+	0	0	+	0	+	?	?	12 hr.	+	Died 3 days after admission; autopsy: septal infarct, mural thrombosis in right auricular appendage, pulmonary emboli

A probe introduced into the upper part of the myocardium at the posterolateral aspect of the left ventricle passed easily from the middle of the myocardium, emerging at the previously mentioned erosion in the epicardium near the apex. The first sagittal cut, made midway between the erosion and the upper portion of the left ventricle, revealed about 5 c.c. of moderately congealed dark red blood trapped in the interstices of the myocardial wall. Moderate sclerosis was present in the other coronary arteries, and there was some narrowing of the left descending coronary artery about 6 cm. from its origin, but no other thrombi were present.

Anatomic Diagnosis.—

Gross: Coronary sclerosis, thrombosis of the left circumflex coronary artery, acute myocardial infarction of the posterior and lateral aspects of the left ventricle, and incomplete rupture of the ventricle into the pericardial sac, with hemopericardium and cardiac tamponade.

Microscopic: (1) Advanced atherosclerosis of coronary arteries with recent rupture of an atheromatous plaque in the circumflex artery, and acute coronary thrombosis. Early fibroblastic activity at point of attachment and beginning endothelial proliferation would suggest the age of the thrombus to be about two to six days. No conclusive evidence of extension proximally was seen, since no fibroblastic activity was seen in thrombus 4 mm. proximal to point of occlusion. (2) Extensive myocardial infarction, with marked neutrophilic reaction and early focal fibroblastic activity (age, about two to six days). Several small, fresher infarcts, without reaction at edges of larger infarct, were observed. The largest one extended from the endocardium to the epicardium in the apical half of ventricle. (3) Extensive hemorrhage into the large infarct, with evidence of some continuity with circulating blood, since there was thrombus formation in some of the hemorrhagic masses in the myocardium, of a type which forms only in circulating blood.

CASE 19.—A 33-year-old man entered the hospital on Dec. 20, 1946, complaining of precordial pain. About two months before entry, the patient noted dull aching pain in the precordial region, brought on by exertion. This distress progressed gradually, and one month later, became relatively constant in character, with radiation to both sides of the neck, shoulders, arms, and occasionally to the back; the pain was aggravated by deep breathing. The patient walked about at night to relieve the pain, without much success. For about three years the patient was known to have had moderate hypertension and tachycardia. There was occasional palpitation, but no dyspnea. In 1938, a thyroidectomy for thyrotoxicosis was performed.

Physical examination revealed the patient to be well developed and obese, and lying quietly in bed. The heart did not appear to be enlarged; the rhythm was regular; the rate, 132; the blood pressure, 120/95; and the second pulmonic greater than the second aortic sound. The heart sounds were distant. The remainder of the examination was essentially negative. An electrocardiogram showed sinus tachycardia with sagging $S\text{-}T_1$ and $S\text{-}T_2$ and flattened T waves. An x-ray film of the chest showed cardiac enlargement. On the day following entry, the patient had an acute attack of precordial distress and presented manifestations of shock, although the blood pressure was 132/94. Subsequently, he was treated with sedation, heparin, and dicumarol. With the exception of a rise in temperature following this attack, the course thereafter appeared satisfactory, and the prothrombin time was adequately elevated. At about 2 A.M. on January 5, the patient developed dyspnea and thereafter rapidly became comatose. He died at 3:25 A.M. Jan. 5, 1947.

Autopsy: The serous surfaces of the pericardium were smooth and glistening, but the sac contained approximately 120 c.c. of turbid yellowish fluid. The heart weighed 470 grams. There was moderate dilatation of the right ventricle and an area of apparent softening over the left apical region. On section, a post-mortem clot was noted in both chambers. The right ventricle measured 3 mm. in thickness and the left ranged from 16 mm. at the base to 2 mm. at the apex. The thinned portion of the apex of the left ventricle, for a distance of 4 cm., was discolored by reddish brown to bright yellow necrosis, and this process extended to the lower half of the interventricular septum, over an area measuring 5 centimeters. These changes were obviously due to myocardial infarction. Elsewhere, the muscle was firm and beefy red. No mural thrombu
s

was noted. The main branch of the left coronary artery, at a point 1.5 cm. from its origin at the level of its bifurcation into the circumflex and descending branches, showed occlusion by a firm grayish brown fixed thrombus, which obtruded upon the orifice of the circumflex branch and continued into the descending branch for a distance of 2 centimeters. Beyond this point, at which some calcification was noted, atheroma was slight in degree and the vessel lumina were patent. The right coronary was not remarkable.

DISCUSSION

An exact comparison between the "treated" and the control group cannot be made, since autopsies were obtained in only three of the eight control patients who died. Of the controls, the patient in Case 12 showed septal infarction, mural thrombosis, and multiple pulmonary emboli. The patient in Case 18 showed old infarction involving the left apex of the heart, and a recent infarct involving the posterior portion of the left ventricle as well as the intraventricular septum. Overlying the septal infarct was a large mural thrombus. The patient in Case 25 showed infarction of the intraventricular septum, thrombosis of the right auricular appendage, pulmonary emboli, and multiple small pulmonary infarcts. Of the five remaining cases, one died in shock sixty-eight hours after admission, the second probably died of pulmonary infarction on the eighth day. The third died of shock eighteen hours after admission, and the fourth died of classical symptoms of pulmonary infarction on the nineteenth hospital day, while apparently improving. The fifth patient, who had persistent dyspnea throughout his illness, died suddenly on the twenty-eighth day. An autopsy was not obtained in this case.

From Table I, it would seem that only one (Case 10) of the treated patients developed any signs suggestive of embolic phenomena (transient facial palsy and aphasia lasting twenty-four hours). These signs were noted when the prothrombin concentration was not sufficiently depressed. This patient's complete recovery and the brevity of symptoms suggested vasospasm rather than embolism as the cause of the neurological signs. Embolic phenomena occurred in six of the untreated patients in from two to nineteen days after the onset of coronary thrombosis.

Three of the treated patients showed evidence of hemorrhage. One patient (Case 13), who died eighteen hours after admission, was found to have rupture of the epicardial surface of the heart with 200 c.c. of blood in the pericardium. It is doubtful, however, that this rupture was due to the anticoagulant therapy, for the patient had received heparin for only twelve hours, and the clotting time one-half hour before death was only 7.5 minutes by the Lee-White method. The prothrombin time at the initiation of treatment (100 mg. dicumarol) was 12 seconds, with a control of 12 seconds.

Another patient (Case 20) developed gross hematuria when the prothrombin concentration fell to 13 per cent of normal. Red blood cells disappeared from the urine after the administration of 60 mg. of menadione intravenously. The patient in Case 21 showed one tarry stool when the prothrombin concentration fell to 17 per cent of normal. The patient was given no specific therapy, and no further evidence of hemorrhage was noted.

All patients have been followed in the Outpatient Dispensary of the Cincinnati General Hospital, the longest follow-up being one year and the shortest, one month. There have been recurrent myocardial infarctions in three of the treated and in one of the untreated patients. In the treated patients, the infarcts recurred two months, three months, and five months, respectively, after the patients' discharge from the hospital. In the untreated patient, the new infarct occurred two weeks after hospital discharge.

SUMMARY AND CONCLUSIONS

1. Combined heparin-dicumarol therapy has been used in twenty-five cases of acute myocardial infarction: twenty in the Cincinnati General Hospital and five in private hospitals.

2. The control group of twenty-five patients was obtained by omitting anticoagulants in every other patient with myocardial infarction admitted to the hospital. Supportive treatment was identical in the treated and untreated cases.

3. Although the series of cases is too small, and the variables of the disease itself too wide to make statistical analysis significant, it appears that the use of heparin-dicumarol adds no additional hazard to the treatment of acute myocardial infarction.

4. There were eight deaths in the control series of twenty-five cases (32 per cent) and three deaths in the series of twenty-five cases (12 per cent) treated with anticoagulants.

5. Autopsies were performed on the three treated cases who died. Neither mural thrombosis nor embolism was present, although two of the patients died within forty-eight hours after the onset of symptoms. One patient showed incomplete rupture of the ventricle with hemorrhage into the pericardium.

6. Emboli occurred in six of the twenty-five cases in the control series (24 per cent), and possibly in one of the twenty-five cases treated with anticoagulants (4 per cent).

ADDENDUM

Since this manuscript was submitted, nineteen additional patients have been treated with anticoagulants and nineteen controls have been observed. Thus, forty-four patients have received anticoagulants and forty-four have served as controls. The mortality in the untreated group was 45 per cent; in the patients treated with anticoagulants, 20 per cent. In the control group, thromboembolic complications occurred in 27 per cent; in the group receiving anticoagulants, in 7 per cent.

Dr. Pearl Zeek performed the autopsies on Cases 9 and 13, and Dr. Edward Gall on Case 19.

Dr. T. J. LeBlanc, Professor of Preventive Medicine, College of Medicine, University of Cincinnati, helped in the preparation of the tables.

Miss Lois Ames and Miss Jean Noertker gave technical assistance.

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THE DETERMINATION OF THE PROGNOSIS OF PREGNANCY IN RHEUMATIC HEART DISEASE

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THE opportunity to observe the clinical behavior of women with rheumatic heart disease who go through pregnancy made it possible for us to examine and evaluate the criteria recommended for selecting the good from the poor risks. One of the earliest studies in this field was made in 1878 by MacDonald[1] who, on the basis of thirteen of his own cases and the reports of eighteen cases by others, emphasized valvular defects and certain specified symptoms as important guides to prognosis. Much progress has since been made in establishing more dependable aids, and it is of interest that MacDonald's pessimism, understandable in the face of a 55 per cent mortality, has to a large extent disappeared. Credit for much of the advance made toward clearer thinking and sounder clinical judgment belongs to James Mackenzie, who approached the problem from the point of view of cardiac functional capacity. In 1921 he wrote,[2] "Estimation of the significance of murmurs, as of all other signs, should be based not on the murmur itself, but on the functional efficiency of the heart . . . . When ten or fifteen years after the causative rheumatic attack . . . the response to effort is good, then the outlook is favorable . . . . When there is marked inefficiency of the heart, shown by breathlessness on slight exertion, rapid pulse, or easily excited palpitation, then there is danger in pregnancy."

Most of the papers in the past twenty-five years support, amplify, or translate into more specific terms Mackenzie's basic rules; none question their validity. In general, the criteria for prognosis as advocated by most authors may be grouped as follows: (1) The amount and degree of structural damage to the heart; (2) the functional capacity of the heart; (3) arbitrary factors, such as age, history of previous failure, and auricular fibrillation.

Not all observers are in agreement as to the relative significance of each of these clinical features. Indeed, several presumably conflicting opinions seem to exist. (These considerations will be taken up in the discussion.) In our experience many of the enumerated signs were found to be very useful, others less so. But it became clearer as our observations accumulated that when these various and apparently unrelated criteria were considered as part of a more inclusive factor, they attained increased meaning and usefulness. This factor

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lies in determining where in the course of the natural history of rheumatic heart disease the individual patient belongs, and this has become the basic principle by which we make our decision. From this, one may prognosticate what the subsequent course is likely to be. Allowance has to be made for the additional work to be done by the heart during the second half of pregnancy. In primiparous women this increment may be difficult to gauge by clinical means, but in multiparous women the previous pregnancy usually constitutes a functional test of the capacity of the heart to do this extra amount of work.

In utilizing this principle one presupposes a familiarity with the course of rheumatic heart disease. Such knowledge is available and has been admirably presented by Cohn and Lingg[3 a,b] of the Research Committee of the New York Heart Association. This will be discussed more fully in the latter part of the paper. One also presupposes, and this is of fundamental importance, that pregnancy itself does not alter the natural history of the disease. This we believe to be true and we will present evidence to support such a contention. We also believe that it has not been demonstrated that one or more pregnancies, if completed uneventfully, shorten the life of the patient.

In determining prognosis according to the position of the patient in the course of her rheumatic heart disease, some degree of uncertainty will, of course, limit the physician's prediction. He is, after all, applying a general rule based upon observations on many thousands of patients to a single individual. But the magnitude of error inherent in this method we will show to be no greater than in the others. There are, on the other hand, several advantages to recommend it. It lends rationale to rules which heretofore seemed arbitrary. For example, auricular fibrillation, universally accepted as an unfavorable sign, is of grave prognosis not because the arrhythmia per se is hazardous, nor because it presents therapeutic difficulties, but because, as has been pointed out by DeGraff and Lingg,[4] it indicates that the patient has reached an advanced stage in her disease. Another example is the history of heart failure in the past, which has a similar implication as will be seen later. This method of determining prognosis also gives a cohesiveness to the several unrelated rules previously used and simplifies them in a manner which facilitates clinical application. Finally, it enables the physician to predict several years in advance, as he is often asked to do when consulted premaritally, whether or not pregnancy will be reasonably safe at a given time in the future. It should be added that a recrudescence of rheumatic fever may alter and accelerate the course of the illness and thus invalidate an opinion based on the assumption that the heart disease would remain inactive. This would constitute a serious limitation were it not true that exacerbations of rheumatic fever are rare during the childbearing period.

This paper is essentially an exposition of this basic principle of determining prognosis of pregnancy not by several arbitrary rules or physical signs alone, but by establishing what position the individual patient occupies in the natural course of rheumatic heart disease.

CLINICAL MATERIAL

A prenatal cardiac clinic was established at Bellevue Hospital in 1939, and has been conducted jointly by the Departments of Medicine and Obstetrics of the Third (New York University) Division. Sessions were held in the general prenatal clinic, making it convenient for the patient to be seen by the obstetrician and the cardiologist during the same visit.

Each patient included in this series was examined and studied by the authors.* The interval between visits varied from one week to one month, depending on the period of gestation and the cardiac status. Special attention was given to the history of rheumatic fever and, when possible, reports were obtained from other hospitals and clinics concerning the patient's previous rheumatic manifestations and the course of her heart disease. In addition to the data on weight, height, blood pressure, hemoglobin, urinalysis, and Wassermann test, the vital capacity under uniform basal conditions was also determined at each visit. Teleroentgenograms and electrocardiograms were taken of the patients in the early and late ante-partum and again during the post-partum period. In cases where the diagnosis was in doubt a stethogram and esophogram were used as diagnostic aids. The final cardiac diagnosis was made by the same observer (J.J.B.) in conformity with the criteria set by the New York Heart Association.[5] This observer studied the course of adult rheumatic cardiac patients in one of the member-clinics of the New York Heart Association for many years.

From October, 1939, to July, 1945, 131 women were observed through pregnancy and puerperium. In eleven other cases pregnancy was interrupted because the prognosis was considered unfavorable.† In each of these cases sterilization was urged, for it was felt that one who was already a poor risk would be unlikely to improve as her heart disease advanced.

The 131 patients were delivered of 133 babies. These included four mothers who gave birth to twins and two mothers who died undelivered. There were eighty-three spontaneous deliveries, thirty-nine forceps, and eight breech deliveries. Cesarean section was performed on three patients for strictly obstetrical reasons. We could see no indication to recommend this procedure on a cardiac basis.‡

OBSERVATIONS

Maternal Mortality.—Table I lists the maternal mortality rate from rheumatic heart disease reported in the literature from 1936 to 1946, inclusive. Re-

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*A number of patients failed to attend the ante-partum clinic and were seen by us for the first time at term on the obstetrical wards. No patient with rheumatic heart disease delivered on our obstetrical service was excluded from this series.

†During the four years preceding the period of this study, from 1935 to 1939, thirty abortions were done for patients with rheumatic heart disease.

‡The presence of rheumatic heart disease, per se, is no longer acceptable as an indication for cesarean section. It may occasionally be resorted to as a means of terminating prolonged labor in order to reduce the danger of heart failure. Authors reporting their own results in groups of patients where cesarean sections were done frequently as compared with those where it was done infrequently agree that the fatality rate is higher in the former group.[6,7] This may be attributed in part to the fact that the greater risks were more likely to undergo section. It is, therefore, important to note that among patients with heart disease of equal severity (Classes 3 and 4) the death rate is significantly higher in the group delivered abdominally (hysterotomy or cesarean section) than vaginally.[8]

ports prior to 1936 were not included since they have been collected and published by Jensen.[28, p.128] Those after 1936 show a striking reduction in mortality rates; from 9.38 per cent for the period between 1890 to 1922 to 3.24 per cent from 1936 to 1946. This advance is very likely a result of better understanding

TABLE I. REPORTED DEATHS AMONG PREGNANT WOMEN WITH RHEUMATIC HEART DISEASE (1936 TO 1946)

AUTHORS	YEAR	NO. OF PATIENTS	NO. OF DEATHS	PER CENT DEATHS
Hay[9]	1936	66	1	1.5
Henderson[10]	1936	76	2	2.6
Hagedorn[11]	1937	50	5	10.0
Harris[12]*	1937	100	8	8.0
Lamb [13]	1937	102	7	6.9
McClure[14]	1937	69	3	4.3
Naish[15]	1937	427	11	2.6
Pardee[16]†	1937	50	1	2.0
Carr[17]	1938	44	1	2.3
Turino and Antony[18]	1938	102	6	5.9
Lange[19]	1939	322	6	1.9
Clahr, Klein, and Greenstein[20]	1940	181	4	2.2
Jensen, Wegner, Keys, and Smith[21]	1940	108	8	7.4
Gorenberg and McGleary[22]‡	1941	345	10	2.9
Hamilton and Thomson[6]	1941	781	37	4.7
Bramwell and Longson[23]	1942	312	22	7.1
Brown and Sage[7]	1942	32	1	3.1
Gorenberg[24]	1943	223	8	3.6
Jones[25]	1943	74	4	5.4
Sampson[26]	1943	60	0	0.0
Mendelson[8]	1944	1,089	8	0.7
Scott[27]	1944	114	3	2.6
Bunim and Rubricius	1947	142	2	1.4
Total		4,869	158	3.24

*Only deaths occurring within thirty days post partum were included in this table.

†Three additional deaths occurred after discharge from hospital from subacute bacterial endocarditis, coronary thrombosis, and "unspecified cause," respectively.

‡The authors state that 95 per cent of the patients had rheumatic heart disease.

of heart disease and its treatment, more skillful and conservative obstetrical management, a closer cooperation between the obstetrician and the internist, and the advent of chemotherapy. Some reports from abroad have not been included because they are still unavailable in this country. Other reports, both foreign and American,[29-38] could not be included because the authors did not specify the type of heart disease present either among the total number of patients or among those that died, or both. It should not be assumed that all deaths listed were from rheumatic heart disease, since many writers made no distinction between the deaths resulting from the heart disease and those due to causes unrelated to it.

As will be noted, in our group there were two maternal deaths. One of our patients, 20 years of age, died of a staphylococcic bacteremia during the fifth month of her first pregnancy. There was no discoverable focus of infection. The other patient, 33 years of age, died of heart failure in the ninth month of her seventh pregnancy. This patient was first seen by us at the end of her sixth pregnancy. At this time she manifested symptoms of diminished cardiac reserve and sterilization was therefore advised. The patient did not consent to this procedure, left the hospital, and did not report for post-partum care. She reappeared during the twenty-seventh week of her next (seventh) pregnancy and was then in congestive failure. Immediate hospitalization was urged in vain. The next day she was admitted in pulmonary edema. After several days of intensive treatment her condition improved. She was advised to remain in the hospital until term but she refused to do so. Several weeks later, the physician who had attended her at home reported that she died undelivered.

Infant Mortality.—The infants delivered on the obstetrical service of Bellevue Hospital during the period of our study were classified for the purpose of this analysis into three groups: infants of mothers with normal hearts, infants of mothers with rheumatic heart disease without failure, and infants of mothers with rheumatic heart disease with failure (Table II and Fig. 1). The mortality rate for infants of mothers with compensated heart disease was not significantly higher than for infants of normal mothers. The mortality rate for infants of mothers with congestive heart failure, however, was 30 per cent, whereas in the compensated group it was 9 per cent and in those with normal hearts, 7 per cent. This difference seems striking, although the number of patients with failure was only eighteen; larger groups would have to be analyzed to establish its significance. Actually, the difference and the standard error between the compensated and decompensated groups just falls short of being statistically significant (21 ± 11.1).

Congestive Heart Failure.—Eighteen of the 131 patients developed congestive failure during pregnancy, an incidence of 14 per cent.* Failure occurred most frequently during the second half of pregnancy (Table III). It should be noted that more instances of failure occurred in the last lunar month than in any preceding month.

*The criteria for congestive failure were pulmonary edema, paroxysmal nocturnal dyspnea, basal râles, or a palpable, tender liver.

TABLE II. EFFECT OF HEART FAILURE ON INFANT MORTALITY: PERCENTAGE DISTRIBUTION

	INFANTS DELIVERED OF NORMAL MOTHERS OCT. 1939 TO OCT. 1943		INFANTS DELIVERED OF MOTHERS WITH HEART DISEASE BUT NOT IN FAILURE		INFANTS DELIVERED OF MOTHERS IN HEART FAILURE	
	NO. INFANTS	PER CENT	NO. INFANTS	PER CENT	NO. INFANTS	PER CENT
Total number of infants delivered	6,263	100	115	100	18	100
Born at term alive and well	5,452	87	97	84	12	66
Premature births alive and well*	392	6	8	7	1	6
Stillbirths, viable	129	2	3	3	2	12
Stillbirths, nonviable†	174	3	5	4	1	6
Neonatal deaths‡	116	2	2	3	2	12

*Infants whose birth wt. was 5 lbs. or less were considered premature.

†Infants weighing less than 3 lbs. were classified as nonviable.

‡Neonatal deaths included babies who died within forty-eight hours after birth.

TABLE III. EFFECT OF ADVANCING PREGNANCY ON HEART FAILURE

WEEKS OF GESTATION	NUMBER OF PATIENTS IN FAILURE
1– 4	0
5– 8	0
9–12	0
13–16	0
17–20	3
21–24	1
25–28	3
29-32	2
33–36	3
37–40	5
Post partum	1

The expected date of delivery was taken as the end of fortieth week of gestation.

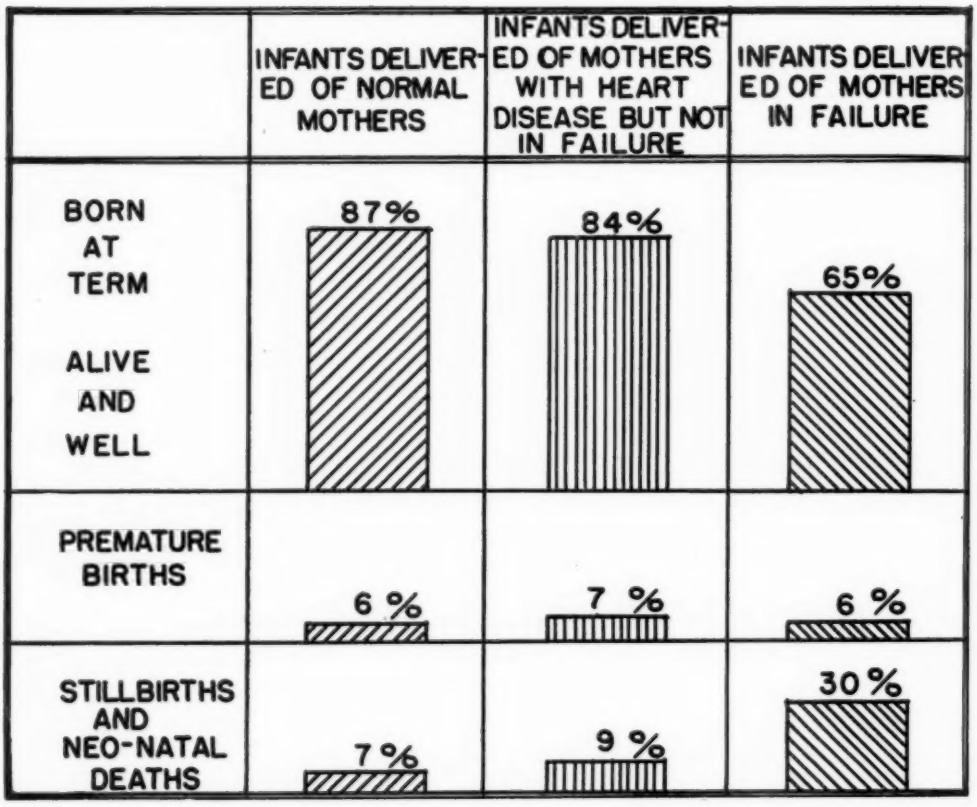

Fig. 1.—Effect of heart failure on infant mortality, percentage distribution.

The interval of time from the onset of the first rheumatic manifestation to the observed pregnancy was determined in 103 patients (Table IV).* As the interval lengthened, the incidence of failure increased. Of those who had had rheumatic fever for less than ten years, 4 per cent went into failure; whereas, of those who had had it longer than fifteen years, 18 per cent or more became decompensated. Patients who failed had heart disease for an average duration of seventeen years, five years longer than those who did not fail. The average age of the group in failure was 27.8 years; of the other group, 24.3 years (Table V). Our data show that about one-fourth of the patients above the age of 30 years, or those who had had rheumatic fever for more than twenty years, developed congestive failure during pregnancy.

A close relationship was observed between the limits of cardiac reserve that existed before pregnancy and the incidence of failure during pregnancy. Only

*In the other cases, there was either no initial episode or the patient did not remember it.

one of the eighty-two patients in Class I and Class II* had congestive heart failure, whereas seventeen of the forty-nine patients in Class III and Class IV presented this complication (Table VI).

TABLE IV. EFFECT OF DURATION OF DISEASE ON HEART FAILURE

DURATION IN YEARS	TOTAL PATIENTS IN GROUP	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE	PER CENT PATIENTS IN FAILURE
0- 9 .	26	25	1	4
10–14	32	28	4	13
15–19	32	26	6	18
20 and over	13	10	3	23
Average duration	—	12.0 years	17.0 years	—
Duration unknown*	28	24	4	14

*Patients who did not know they had heart disease until coming to clinic or without a history of previous rheumatic manifestations.

TABLE V. EFFECT OF AGE ON HEART FAILURE

AGE GROUPS IN YEARS	TOTAL	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE	PER CENT PATIENTS IN FAILURE
Under 20	20	18	2	10
20–29	78	69	9	12
30–39	29	23	6	20
40 and over	4	3	1	25
Average age	—	24.3	27.8	—

A history of previous failure was likewise found to be significant. Every patient who decompensated during a previous pregnancy did so again during the observed pregnancy. However, 9 per cent of those who had never had failure before developed it during the observed pregnancy (Table VII).

It has been stated that when the aortic valve is damaged the patient faces a greater risk during pregnancy than when the mitral valve alone is involved.[15,28,39] Our experience does not confirm this observation. Table VIII shows that failure

*The classification of the New York Heart Association was used:[5]

Class I: Patients with cardiac disease and no limitation of physical activity;
Class II (formerly 2a): Patients with cardiac disease and slight limitation of physical activity;
Class III (formerly 2b): Patients with cardiac disease and marked limitation of physical activity;
Class IV: Patients with cardiac disease and who are unable to carry on any physical activity without discomfort.

was more than twice as common in patients with mitral valvular disease alone (24 per cent) than it was in those who had aortic or combined aortic and mitral valvular disease (11 per cent).

TABLE VI. EFFECT OF FUNCTIONAL CAPACITY ON FAILURE

FUNCTIONAL CLASSIFICATION*	TOTAL PATIENTS	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE	PER CENT PATIENTS IN FAILURE
Class I	37	37	0	0
Class II	45	44	1	2
Class III	47	32	15	32
Class IV	2	0	2	100
Total	131	113	18	14

*Classification of the New York Heart Association.

TABLE VII. CORRELATION BETWEEN PREVIOUS HEART FAILURE AND FAILURE IN OBSERVED PREGNANCY

	TOTAL	NUMBER OF PATIENTS WHO DID NOT FAIL IN OBSERVED PREGNANCY	NUMBER OF PATIENTS WHO FAILED IN OBSERVED PREGNANCY	PER CENT PATIENTS WHO FAILED IN OBSERVED PREGNANCY
Patients who had heart failure previously	9	2*	7	79
Patients who had no heart failure in the past	122	111	11	9
Total	131	113	18	14

*These two patients failed during an attack of acute rheumatic carditis and not during pregnancy.

TABLE VIII. EFFECT OF VALVULAR LESIONS ON FAILURE

VALVULAR LESIONS	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE	PER CENT PATIENTS IN FAILURE
Mitral insufficiency with enlarged heart	30	1	3
Mitral stenosis and mitral insufficiency	58	14	24
Aortic insufficiency alone or with other valvular lesions	27	3	11
Total	113	18	14

The size of the heart was determined by teleroentgenograms at several intervals during and after pregnancy in forty-nine patients who did not fail and in ten who did. The maximum transverse diameter of the heart was measured and the per cent enlargement was calculated according to the table of Ungerleider and Clark.[40] The weight of the patient at the time the radiogram was taken was used uncorrected when making the calculations. The results thus obtained approximated the post-partum cardiac measurements within a range of 10 per cent or less. Cardiac measurement by such a method therefore seems reliable, even though the configuration and position of the heart changes as gestation advances. None of the patients whose hearts were enlarged less than 10 per cent above normal had failure. Contrariwise, all patients who failed showed an increase of 10 per cent or more above normal. However, a number of women with 20 to 30 per cent enlargement did not experience decompensation. It was concluded from this that while patients with minimal cardiac enlargement are better risks, those with moderate enlargement are not necessarily bad risks. In so far as these limited observations indicated, there was a general but not a strict correlation between the degree of enlargement and the likelihood of failure.

The prognosis in all patients with rheumatic heart disease, men and women, has been found to be more favorable when the original manifestations consisted of chorea or muscle and joint pains rather than polyarthritis or carditis.[41-44] We have found this to be true also for pregnant cardiac patients. None of the patients who had had chorea or muscle and joint pains as the sole rheumatic manifestation developed failure during the observed pregnancy. Five of the forty-seven patients who had had polyarthritis alone, and six of nine patients who had had both polyarthritis and chorea became decompensated. The average duration from the first rheumatic manifestation to the observed pregnancy in this last group was eighteen years, whereas in the group that had chorea alone it was fourteen and one-half years. This difference may account in part for the greater incidence of failure. Although the groups are not large enough to be

TABLE IX. EFFECT OF PARITY ON HEART FAILURE

AGE GROUP IN YEARS	PRIMIPARA		MULTIPARA	
	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE
Under 20	12	2	6	0
20–29	28	4	41	5
30–39	2	1	21	5
40 and over	0	0	3	1
Total	42	7	71	11
Per cent patients in failure	—	17	—	15

suitable for statistical analysis, nevertheless, this observation seems to us to merit further study since it may have clinical importance. Evidently polyarthritis, or a combination of polyarthritis and chorea, implies severer infection and, hence, greater cardiac damage than chorea alone.

There seemed to be no significant difference in the rate of failure among primiparous as compared with multiparous women (Table IX).

DISCUSSION

The natural history of rheumatic heart disease may be said to consist of four phases: (1) an initial infection which may be manifested by carditis, polyarthritis, chorea, or muscle and joint pains; (2) one or more recrudescences which, like the primary episode, may follow a hemolytic streptococcic infection; (3) an inactive period, lasting usually from puberty or adolescence to the fourth or fifth decade, in which there are usually no recurrences or evidence of decreasing functional capacity; and (4) a diminution in cardiac reserve leading progressively to congestive heart failure and later death. When auricular fibrillation supervenes, it usually occurs during the last phase and is essentially a reflection of the long duration of the disease.

Phase *1*, the initial infection, usually occurs in childhood. It does not always precede heart disease. Twenty per cent or more of adult patients give no history of having had any previous rheumatic manifestations. Phase *2*, recurrences of rheumatic fever, rarely complicates pregnancy. Phase *3*, the period when the heart disease is inactive, is the one during which pregnancy usually occurs and this explains why the majority of patients do well when under intelligent obstetrical care. Phase *4*, diminished cardiac reserve and failure, is seen in less than one-fourth of the pregnancies. It is of utmost importance to recognize when a woman who is pregnant or contemplating pregnancy is approaching this phase. Cardiac failure ranks first among the causes of maternal deaths in patients with heart disease and is the only cause amenable to therapy, especially when detected early. In addition, as has been demonstrated, the chances of having a live baby are dependent to a large degree on the mother not developing heart failure.

How long a given patient is likely to remain in Phase *3* before entering Phase *4* will depend, in the main, on the number of years that have elapsed since the initial infection, the severity and nature of this infection (carditis is more serious than polyarthritis and the latter is more severe than chorea), the frequency and number of recurrences, and the age of the patient. When there is no previous history of any rheumatic manifestation by which to determine the duration of the disease, the absolute age of the patient may be used as a rough index.

Complications such as subacute bacterial endocarditis, embolization, intercurrent infections, and so forth, may occur in any phase and may seriously alter the course of events as here outlined.

Effect of Pregnancy on Duration of Life.—The question of whether pregnancy alters the course of rheumatic heart disease or shortens the life of the patient is

of fundamental importance. In several groups, the reported age of death was younger in nulliparous than in parous women.[28] When the sample was reduced to include only those who lived to a "marriageable age," the same results were obtained.[32,45] When, furthermore, only those who died of congestive heart failure were considered and the group subdivided into those who survived past the age of 18 years and those who survived past the age of 40 years, there was no significant difference in the average age at death between nulliparous and parous women.[45] In this last group, those who died during pregnancy were not included.

The reports just quoted are subject to some criticism. Several important factors in the nulliparous and parous groups were not controlled; these include age at onset of heart disease, number and severity of recurrences of rheumatic fever, functional capacity of the heart, and the respective duration from onset of heart disease to failure and from failure to death. These factors were carefully considered and controlled in an analysis made by Cohn and Lingg[46] who compared the clinical course and life span of 169 women, who bore one or more children after they were known to have developed rheumatic heart disease, with the course of 215 nulliparous women who had the same disease. All patients in both groups were observed in the clinics of the New York Heart Association to the time of death. The groups were comparable in that each consisted of a similar proportion of patients who developed heart disease before the childbearing period (age 19) and after, who had mild heart disease with good functional capacity, and who had severe heart disease with imparied cardiac reserve or episodes of congestive failure. The analysis showed that there was no significant difference in the tempo of the clinical course, the rate of development of congestive heart failure, the duration of life from onset of disease to death, and the age at death in the parous and the nulliparous groups.

This reassuring conclusion applies only to those who survive the period of gestation. Pregnancy entails certain risks for the patient with rheumatic heart disease which one who is not pregnant obviously does not face. Failure or death may occur during or soon after pregnancy which may not have resulted had the patient not been pregnant. Assuming, however, that the patient does survive the pregnancy, the subsequent course will very likely remain unaltered.

Age: Patients with rheumatic cardiac disease, regardless of parity, are more prone to fail as they get older. In a group of 644 adult cardiacs (male and female), the average age of failure was 30 years.[4] It is apparent, then, why many observers[6,22,28,47] have stressed age as an important guide in the prognosis of pregnant cardiac patients. Patients above the age of 30 years, and especially above 35 years, are much more apt to decompensate than those who are younger.

Duration: If the time of onset of heart disease were known, then the duration from onset to pregnancy would undoubedly be more dependable as a prognostic guide than the absolute age of the patient. Lacking this precise information in all cases, we have arbitrarily taken the first rheumatic manifestations as the time of onset. This does not imply that the heart disease necessarily begins at this time. As has been mentioned, there is a closer correlation between duration of disease and failure than between absolute age and failure.

Enlarged Heart: That the heart actually increases in weight during pregnancy has not yet been clearly demonstrated. In women with similar rheumatic valvular lesions who died of congestive heart failure, the heart was found to be of approximately the same weight at autopsy regardless of whether the patients had no, few, or many pregnancies.[45] Thus, it is likely that pregnancy causes no permanent cardiac enlargement. Since the heart increases in size as the duration and severity of the disease increases, the risk of failure is naturally greater in pregnant women whose hearts are markedly enlarged.[13,48-50] Yet heart size, per se, we have found not to be as significant an index of prognosis as other factors here considered.

Valvular Lesions: There is no unanimity of opinion as to the seriousness of the combination of mitral stenosis and aortic insufficiency as compared with mitral stenosis alone. Some observers attach grave significance to the coexistence of mitral and aortic lesions,[15,28,39] and others state that there is no significant difference between the two groups.[49,51] This divergence of opinion also exists among students of rheumatic heart disease in general.[52] Our experience corresponds with those who attribute no greater gravity to combined aortic and mitral valvulitis than to mitral stenosis alone. This is substantiated by the fact that data collected by us from reports published since 1936 show no important difference between the mortality rates among pregnant women with combined mitral and aortic valvulitis and those with mitral valvulitis alone (Table X)

Functional Class and Previous Failure: The functional capacity of the heart to do work is without doubt the most reliable single index of the prognosis in pregnancy. At times, however, it is difficult to establish this with precision and, again, it may vary from one month of pregnancy to another. An actual test of pregnancy is, therefore, more reliable; hence it is evident that a patient who has failed in a previous pregnancy will almost certainly decompensate again unless failure was due to circumstances not likely to recur, such as active rheumatic carditis.[22,54-57] The contrary is not true, that patients who have not failed previously will not fail in a later pregnancy. In our series, 11 per cent of the multiparous patients who had no history of failure decompensated during the observed pregnancy.

Multiparity: Conflicting opinions have been expressed on parity: such as, the prognosis is worse in primiparas;[50] it is worse in multiparas;[15,58] parity, per se, has no important bearing on the prognosis.[47,56] This discrepancy may have resulted from the fact that the different authors did not control to the same degree, at least, two factors that influence the outcome, namely, the duration of heart disease (longer in multiparas) and the physical effort spent in obstetrical labor (greater in primiparas). When allowance is made for both factors, it seems reasonable to conclude that parity, per se, is of no real significance.

There are a number of factors that should be considered in evaluating the prognosis of pregnancy in patients with heart disease. Some of these are more important than others, but each of them fits into a more inclusive principle which is based on the orientation of the patient in the natural course of her heart

disease. The validity of applying this principle to pregnant cardiac patients is supported by the evidence that gestation does not alter the course of the disease.

TABLE X. DEATHS AMONG PREGNANT RHEUMATIC CARDIAC PATIENTS GROUPED ACCORDING TO VALVULAR LESIONS (1936 TO 1946)

	NUMBER OF PATIENTS WITH MITRAL VALVULITIS ALONE	NUMBER OF DEATHS	PER CENT DEATHS	NUMBER OF PATIENTS WITH AORTIC OR AORTIC AND MITRAL VALVULITIS COMBINED*	NUMBER OF DEATHS	PER CENT DEATHS
Hay (1939)[9]	56	1	1.8	10	0	0
Harris (1937)[12]	81	6	7.4	19	2	9.5
Lamb (1937)[13]	89	5	5.6	12	2	16.7
Naish (1937)[15]	349	10	2.9	78	2	3.9
Bramwell and Longson (1939)[23]	260	20	7.7	31	1	3.2
Jensen et al. (1940)[21]	88	6	6.8	11	1	9.1
Hamilton and Thompson (1941)[6]	581	28	4.7	148	8	5.3
Stromme and Kuder (1946)[63]	565	7	1.2	90	1	1.1
Total	2,069	83	4.01	399	17	4.26

*Forty-seven of these 399 patients had aortic valvulitis alone, 352 had combined mitral and aortic valvulitis.

SUMMARY

In determining the prognosis in pregnancy of 142 women with rheumatic heart disease, the following factors were considered: duration of rheumatic fever, age, functional capacity, history of previous failure, type of valvular damage, size of heart, nature of earlier rheumatic manifestations, and parity. It was found that the important signs were those which helped prognosticate congestive failure. That failure is the governing feature in prognosis is supported by the observations (1) that it is the most common cause of death in pregnancy complicated by rheumatic heart disease and (2) that the infant mortality rate for our group of patients with congestive heart failure was three times as high as for patients who had heart disease without failure and four times as high as for normal pregnant women delivered on the same obstetrical service.

The factors found to be important in prognosticating failure and in estimating the risk involved in pregnancy form integral parts of a basic principle, which consists of establishing the patient's position in the natural course of her rheumatic

heart disease. This principle gains validity when data collected under well-controlled conditions indicate that pregnancy per se does not alter the course of this disease. The application of this principle for determining prognosis led to interruption (per vagina) of only eleven of 142 pregnancies. No hysterotomies were performed after the patient was permitted to pass through the first trimester of pregnancy. There were no deaths from congestive heart failure among the 129 patients who remained under our care through pregnancy and parturition.

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NEWER CONCEPT OF STOKES-ADAMS SYNDROME

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STOKES-ADAMS attacks are generally believed to be due to periods of ventricular asystole occurring in patients with heart block. The Criteria Committee of the New York Heart Association defined this syndrome as "attacks characterized by unconsciousness, often accompanied by muscular twitchings and even generalized convulsions. These attacks occur in patients with auriculo-ventricular block when the ventricular diastole is sufficiently prolonged to result in a severe grade of cerebral ischemia. The duration and severity of an attack depend on the length of ventricular diastole. This term is not applied to syncope due to other causes."[1]

White[2, p. 677] described the syndrome as "the association of syncope and convulsions with marked slowing of the heart's action. . . All grades of disturbances of the cerebral circulation may exist from slight dizziness and faintness with transient ventricular standstill of two or three seconds, duration up to extreme degrees of the Adams-Stokes syndrome with cessation of the heart beat for as long as twenty or thirty seconds."

These definitions reflect the widely-held belief that ventricular standstill is the only disturbance of the cardiac mechanism which, supervening in heart block, causes loss of consciousness. However, for many years individual case reports recurring in the medical literature indicated the probability that other cardiac arrhythmias might be responsible for the attack in patients with heart block.*

Finally, Parkinson and associates,[3] in 1941, reviewed all reported cases of Stokes-Adams syndrome in which electrocardiographic tracings were obtained during the attack. Their findings indicate that only 55 per cent of attacks were associated with ventricular asystole. The remainder were due to various combinations of ventricular tachycardia, ventricular fibrillation, and ventricular asystole.

On the basis of this study, Parkinson defined Stokes-Adams disease as the "name applicable to patients with heart block who suffer from recurrent attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these."[3]

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Presented at the Twentieth Scientific Meeting of the American Heart Association, Atlantic City, N. J., June 6 and 7, 1947.

*The authors of these reports will not be cited in this communication since they have been included in a paper by Parkinson and associates.[3]

The following case is reported because it graphically records in a single patient the different arrhythmias which may precipitate a Stokes-Adams attack. It is also presented as additional evidence against the erroneous concept that ventricular asystole is the sole mechanism precipitating these attacks.

CASE REPORT

A colored woman, 70 years of age, was admitted to the hospital because of repeated convulsions during the preceding twenty-four hours. One week previously, she had noted increasing shortness of breath and inability to carry on her usual activities. Otherwise, her history was negative for hypertension, syphilis, anginal attacks, decompensation, or syncopal episodes. She had had approximately fifteen attacks of convulsions before entering the hospital. The onset

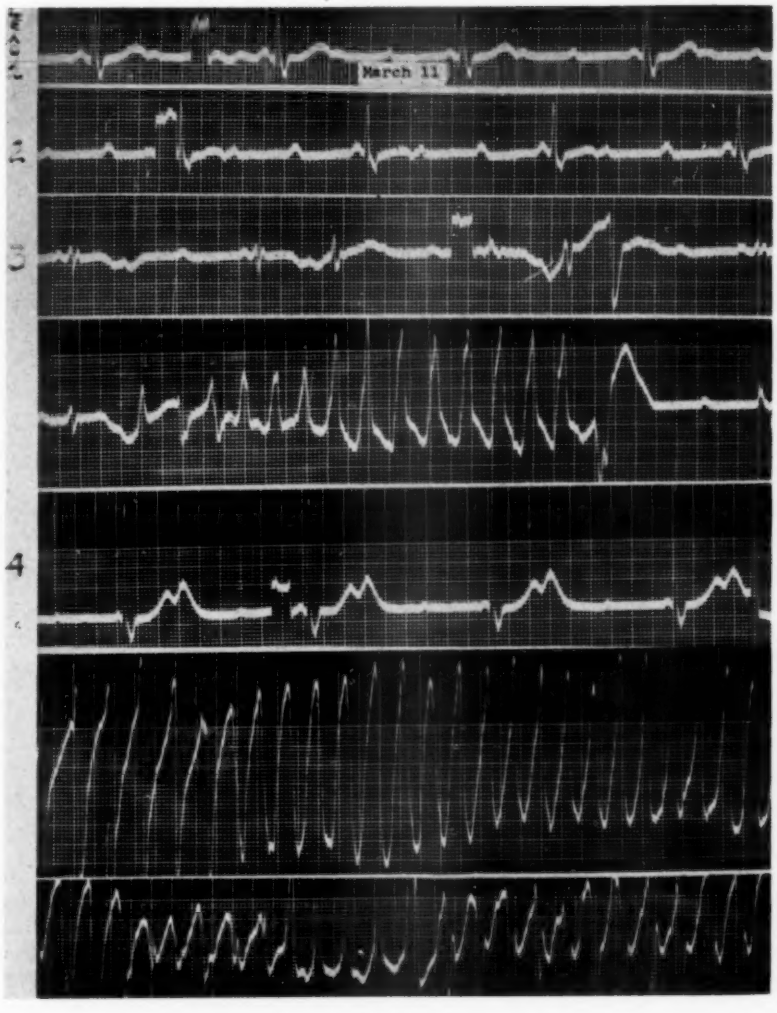

Fig. 1.—Electrocardiogram on admission showing complete auriculoventricular dissociation, with runs of ventricular tachycardia.

of the attack was usually preceded by periods of rapid heart action, which increased in frequency and duration until unconsciousness occurred.

Physical examination in the intervals between convulsions revealed the patient to be in no apparent distress. She was entirely comfortable lying flat in bed. Her heart was not enlarged. The ventricular rate was regular at a rate of 20 beats per minute with an occasional extrasystole. In the intervals between the ventricular beats, fainter beats were audible at 72 per minute, and these were synchronous with the venous pulsation in the neck. The heart sounds were of good quality and no murmurs were present. The arterial pressure was 200/90. There was no evidence of decompensation. Gross neurological examination revealed no abnormality.

The diagnosis was complete A-V heart block with Stokes-Adams syndrome. She was given ephedrine sulfate orally, three-eights of a grain, every three hours. The following morning an electrocardiogram confirmed the presence of complete auriculoventricular dissociation, but also indicated runs of ventricular tachycardia (Fig. 1). The possibility that ephedrine might be responsible for the ectopic rhythm, and might further precipitate ventricular fibrillation, caused us to discontinue the drug and prescribe quinidine sulfate in doses of 15 grains four times daily. During the next few days, electrocardiographic tracings were obtained during many Stokes-Adams attacks. The patient was asymptomatic during the periods of complete heart block, but cerebral manifestations were likely to occur when other cardiac arrhythmias supervened. These arrhythmias, recorded during several different attacks, included the following: ventricular fibrillation followed by ventricular tachycardia (Fig. 3); ventricular tachycardia followed by ventricular asystole (Fig. 3); ventricular asystole alone (Fig. 2); ventricular tachycardia followed

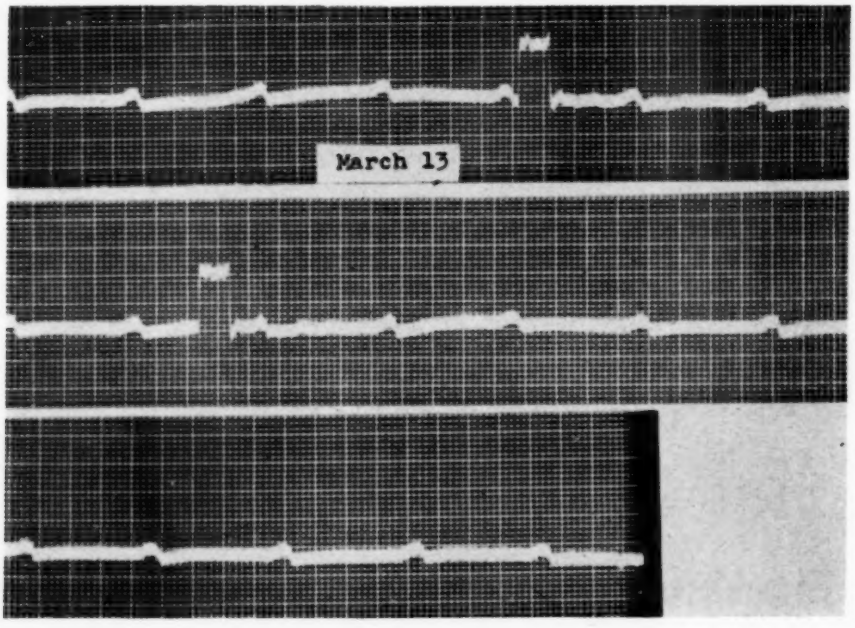

Fig. 2.—Continuous tracing of Lead II showing ventricular asystole of fifteen seconds during a Stokes-Adams attack.

by ventricular fibrillation, ventricular tachycardia, and ventricular asystole (Fig. 3); and finally, ventricular tachycardia followed by ventricular fibrillation and ventricular asystole (Fig. 4).

During the first three days, it was apparent that the patient was becoming worse in spite of a total intake of 132 grains of quinidine, and that this drug could not prevent ventricular tachycardia and fibrillation in her case. It was then decided to treat the block rather than the ectopic

rhythms (Table I). Realizing full well the theoretical contraindication, 1.0 c.c. of a 1:1000 solution of epinephrine was administered into a vein slowly. The patient had no Stokes-Adams attacks during the next hour. Therefore, another 1.5 cc. of epinephrine were given intravenously with no unusual effects. The absence of Stokes-Adams attacks led us to continue epinephrine and ephedrine therapy. During the next five days, the patient was free of attacks, and her improvement was so striking that preliminary arrangements were made to discharge her from the

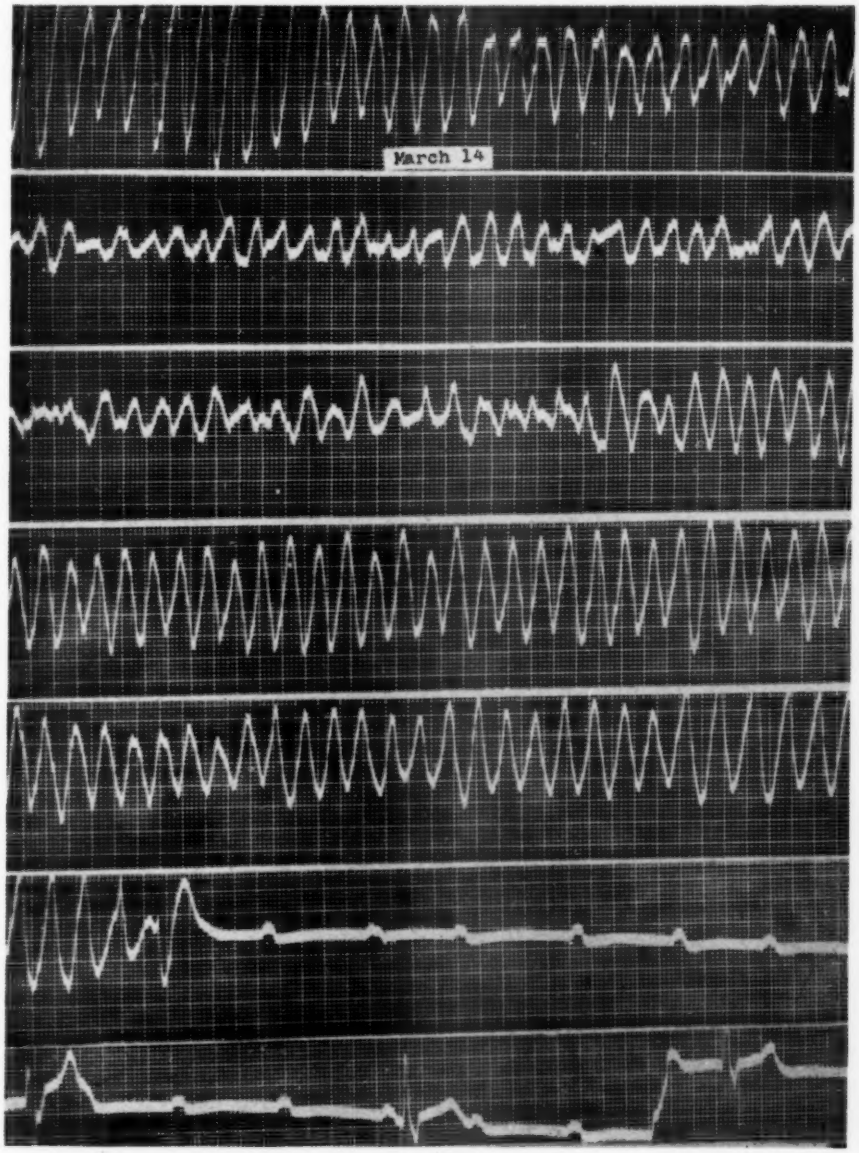

Fig. 3.—Continuous tracing of Lead II during Stokes-Adams attack showing ventricular tachycardia, ventricular fibrillation, ventricular tachycardia, ventricular asystole, and return to basic rhythm (complete heart block).

hospital. On the morning of the sixth day of epinephrine therapy, the patient developed a right hemiplegia and a temperature of 102° Fahrenheit. Later that day, râles appeared in the bases of the lungs, the patient became comatose, the temperature rose to 104.5° F., and she succumbed the following morning. The electrocardiogram obtained the afternoon before exitus (Fig. 5) revealed no significant changes from the original electrocardiogram. The progressive increase in rate of the auricular and ventricular complexes following epinephrine therapy is evident in Fig. 6.

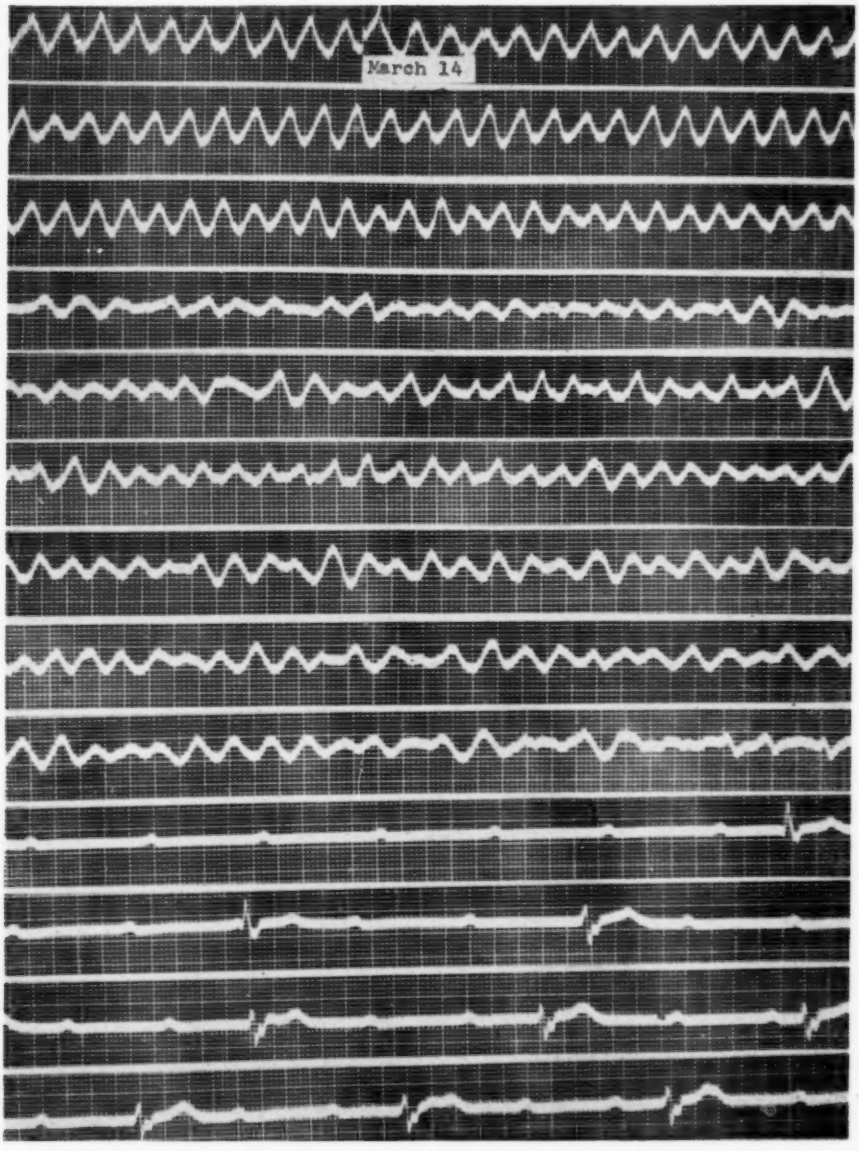

Fig. 4.—Continuous tracing of Lead II during Stokes-Adams attack showing ventricular tachycardia, ventricular fibrillation (forty-one seconds), ventricular asystole, and return to basic rhythm (complete heart block).

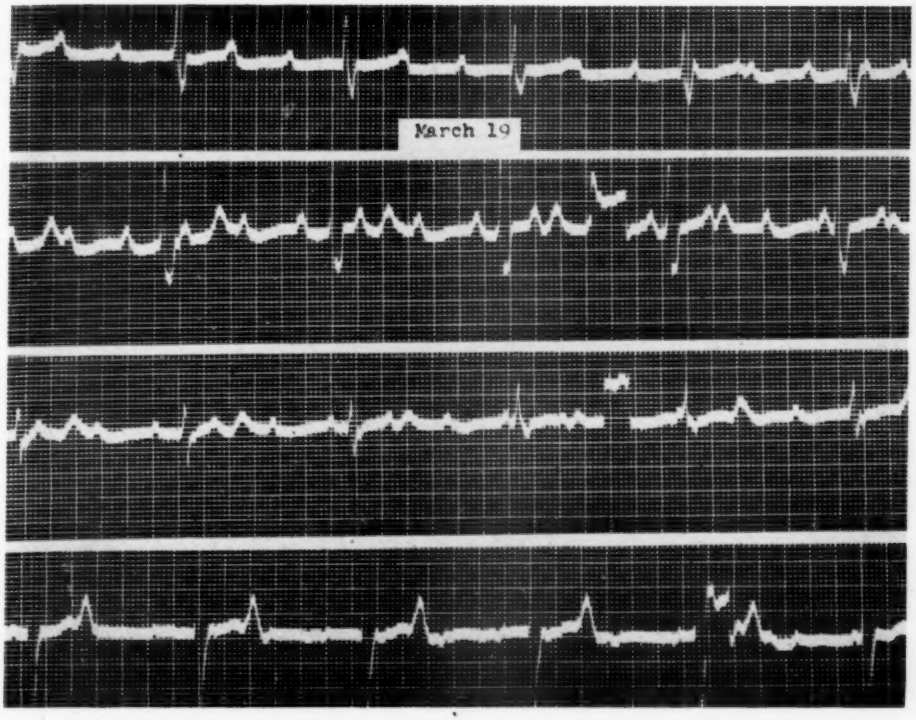

Fig. 5.—Electrocardiogram the day before exitus showing complete auriculoventricular dissociation, with an auricular rate of 120 and ventricular rate of fifty per minute. The contours show no significant difference from those taken on admission.

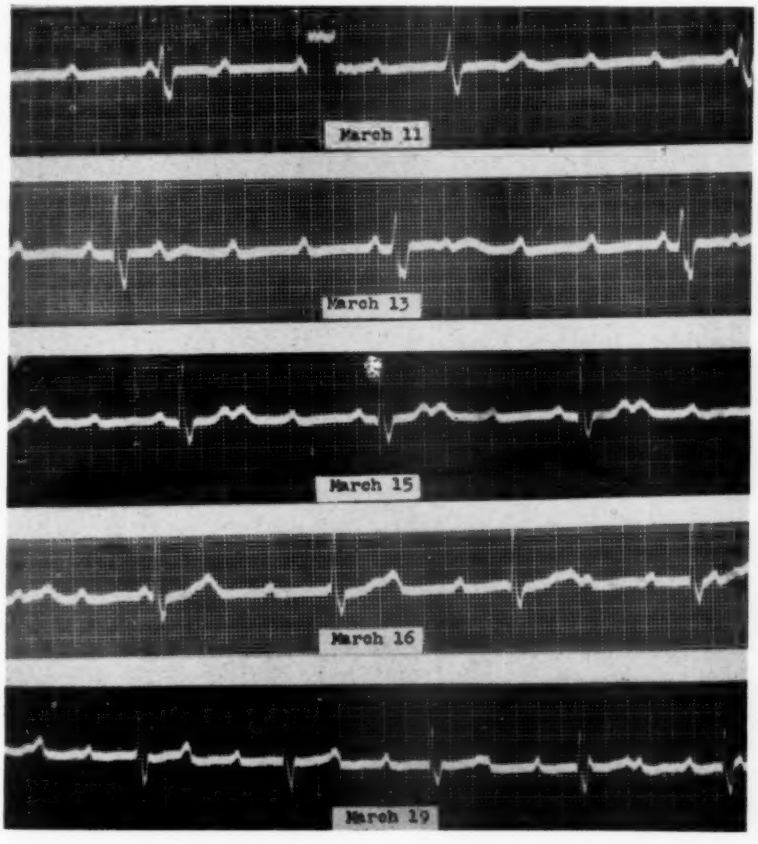

Fig. 6.—Lead II showing progressive increase of auricular and ventricular rates due to epinephrine therapy.

The significant findings at post-mortem examination* were in the brain and heart. The brain revealed slight to moderate generalized edema without evidence of hemorrhage, discoloration, or softening. A moderate amount of atherosclerosis was noted in the arteries, most evident in the basilar vessels. Thrombi were not demonstrable, and no obvious cause for the hemiplegia could be established.

TABLE I. SUMMARY OF CLINICAL COURSE

DATE	CONVULSIONS	DIAGNOSIS	TREATMENT
3-10	Present	* CHB, VA, CHB	Ephedrine gr. 3/8 q 4 hr. (2 doses)
3-11	Present	** CHB, VT, CHB (Fig. 1)	Quinidine gr. 15 Q.I.D.
3-12	Present	*** CHB, VF, VT, CHB	Quinidine gr. 6 q 2 hr.
3-13	Present	*** CHB, VT, VA, CHB *** CHB, VA, CHB (Fig. 2)	Quinidine gr.6 Q.I.D. Total quinidine, gr. 132
3-14	Present	*** CHB, VT, VF, VT, VA, CHB (Fig. 3) *** CHB, VT, VF, VA, CHB (Fig. 4) *** CHB, VT, VF, CHB *** CHB, VF, VT, VF, VA, CHB	1 c.c. epinephrine 1:1000 I.V. 1.5 c.c. epinephrine 1:1000 I.V. 1 c.c. epinephrine oil q 4 hr. Ephedrine gr. 3/8 q 6 hr.
3-15	Absent	** CHB	1 c.c. epinephrine oil q 4 hr. Ephedrine gr. 3/8 q 4 hr.
3-16	Absent	** CHB	1 c.c. epinephrine oil q 4 hr. Ephedrine gr. 3/8 q 4 hr.
3-17	Absent	** CHB	1 c.c. epinephrine oil q 4 hr. Ephedrine gr. 3/8 q 4 hr.
3-18	Absent	** CHB	1 c.c. epinephrine oil q 4 hr. Ephedrine gr. 3/8 q 4 hr.
3-19	Absent	** CHB * Right hemiplegia Temp. 102°	Ephedrine gr. 3/8 q 4 hr.
3-20	Absent	** CHB * Right hemiplegia "Hypostatic pneumonia" Temp. 104.6°—Expired	

* Clinical diagnosis
** Electrocardiograph diagnosis
*** Electrocardiograph diagnosis of Stokes-Adams attack

CHB—Complete heart block
VT —Ventricular tachycardia
VF —Ventricular fibrillation
VA —Ventricular asystole

The heart size was within normal limits. Both coronary ostia were markedly narrowed by atherosclerotic plaques. Approximately 3.5 cm. from the origin of the left coronary artery, the lumen of the anterior descending branch was narrowed to one-fourth its size by a sclerotic plaque 2.0 cm. long. The right coronary artery also contained a sclerotic plaque 4.0 cm. from the ostia which encroached upon the lumen. Gross examination revealed no thrombi, areas of infarction, or fibrosis. Sections through the auriculoventricular node and bundle of His revealed an area of fibrosis and hyalinization which appeared somewhat atypical (Fig. 7). Sections were cut, there-

*Post-mortem examination was performed by Doctors S. A. Wallace and P. Marcuse.

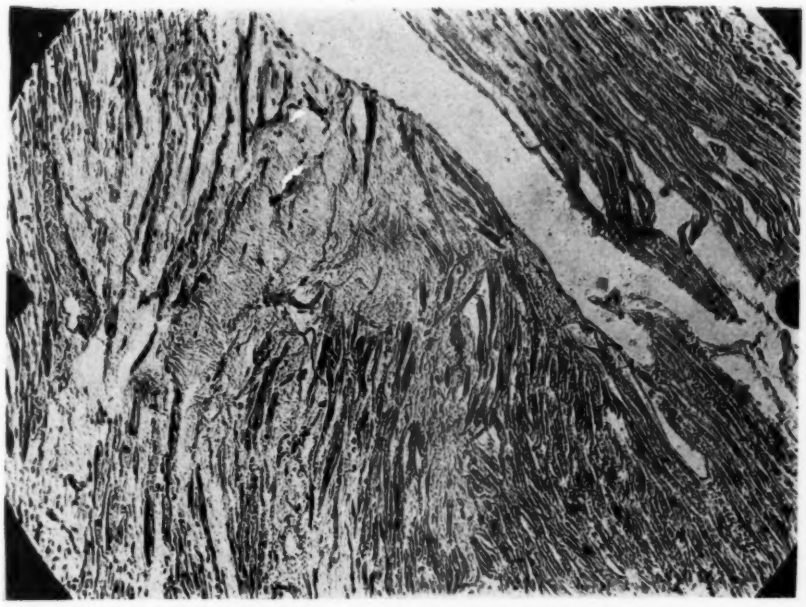

Fig. 7.—Section through A-V node and upper bundle of His showing fibrosis and hyalinization.

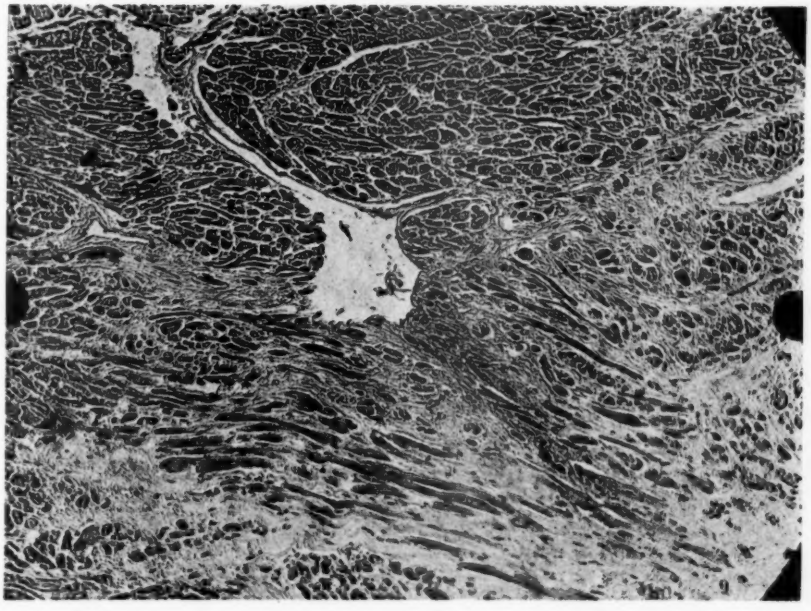

Fig. 8.—Section through A-V node and upper bundle of His in a "normal" heart showing fibrosis and hyalinization similar to Fig. 7.

fore, from normal hearts in the same area, that is, in the junctional tissue just above the interventricular septum behind the posterior aortic valve. These normal hearts revealed a similar type of histologic structure (Fig. 8). Closer study of the gross specimens of the normal and pathologic hearts indicated that our sections included a portion of the fibrous trigone. It was most surprising to us to learn from a review of histology texts that the auriculoventricular node and upper bundle of His are situated in the fibrous trigone.[4] One wonders how many cases reported in the literature as showing fibrosis of the node or bundle of His have actually had a normal histologic structure. Microscopic sections of the lower bundle, and auricular, septal, and ventricular myocardium revealed nothing of significance.

DISCUSSION

Cardiac Mechanism in Stokes-Adams Attacks.—The cerebral anemia precipitating recurrent syncope and convulsions in this case were due not only to ventricular asystole, which is widely believed to be the sole mechanism, but also to rapid ventricular tachycardia, ventricular fibrillation, and to different combinations of these arrhythmias. It is emphasized that this patient's abnormal cardiac mechanism, graphically demonstrated by electrocardiographic tracings during syncope and convulsions, is not unusual, but has occurred in half of the reported cases of Stokes-Adams syndrome in which electrocardiographic tracings were made during the attack.

It is interesting that in the first description of this disease, Morgagni,[5] in 1769, quoted his patient as describing "sudden commotions" and "tumultuary motions" of the precordium immediately prior to the attacks. Stokes' patient also noted a "fluttering sensation about the heart" before his attacks.[6] These sensations are more likely to be due to ventricular extrasystoles and tachycardia than to ventricular standstill, and closely resemble the premonitory symptoms of this case.

Parkinson's definition, which is compatible with the facts and with the historic descriptions of the original cases, is definitely to be preferred to the incomplete, inaccurate definitions in many current textbooks.

Pathologic Anatomy and Physiology of Stokes-Adams Attacks.—It is believed that the auriculoventricular bundle is more sensitive to anoxemia than the undifferentiated myocardium because of its more specialized nature, and its nerve-like function. A partially inadequate vascular supply may cause total functional impairment without causing demonstrable histologic change. Thus, the bundle of His is especially vulnerable in the atherosclerotic age group, in which 80 to 90 per cent of all complete A-V heart block occurs.[7] The marked coronary sclerosis and partial ostial occlusion impeded the coronary flow to a degree sufficient to explain the heart block in this patient.

One possible explanation for the various arrhythmias observed in this case can be given. In other portions of the myocardium (possibly adjacent to the bundle, and supplied by the same artery), there probably existed a relative, or at least potential, myocardial ischemia due to the same coronary sclerosis, plus the additional hazard of an excessively prolonged diastolic period associated with the heart block. Minor physiologic factors adversely affecting relative coronary blood flow, such as slight lowering of aortic pulse pressure, increased

exercise, increased diastolic time, and so forth, factors which cause no appreciable clinical effect in normal individuals because of adequate reserve, grossly exaggerated the coronary insufficiency and precipitated an irritative myocardial anoxemia. This state was reflected in the ventricular extrasystoles, which still further compromised the coronary flow, progressed to ventricular tachycardia, and finally to ventricular fibrillation. The period of ventricular asystole which followed the rapid ectopic rhythm was evidence of myocardial exhaustion. Recovery from this phrase was signaled by an idioventricular beat and return to the basic rhythm. This was the sequence in 70 per cent of the recorded attacks.

Therapy.—The ineffective response to quinidine in this case is consistent with the impression of some clinicians that this drug not infrequently fails to stop or prevent ventricular tachycardia. The present tendency to administer larger and larger doses is an indication that therapeutic failure is not an uncommon occurrence. Whether or not increased dosage will result in greater success awaits further reports. In this case, however, 132 grains of quinidine administered over a period of three days did not prevent ventricular tachycardia and fibrillation. This case poses the question as to whether or not quinidine is the drug of choice in recurrent ventricular tachycardia associated with A-V heart block. Incidentally, a progressively widening QRS complex, which some believe to be a contraindication to further quinidine therapy, was not evident in the tracings.

Epinephrine is known to be a dangerous drug in patients with ventricular extrasystoles and ventricular tachycardia because of the possibility of its initiating ventricular fibrillation. This danger is especially great during cyclopropane and chloroform anesthesia. White[2, p. 683] warns against its use in ventricular asystole when it is preceded by ventricular fibrillation.

However, in this patient, who apparently had the prime contraindications of recurrent ventricular tachycardia and fibrillation and periods of asystole preceded by fibrillation, epinephrine effectively prevented Stokes-Adams attacks and the arrhythmias which precipitated them. One may surmise that the advantageous effect of epinephrine upon the coronary flow (the increased heart rate and decreased diastolic period, increased aortic pulse pressure, increased contractility, and coronary vasodilation) more than compensated for its potential harmful direct effect upon myocardial irritability.

Cause of Death.—Stokes-Adams syndrome predisposes to three modes of cardiac death. Sixty per cent of these patients die suddenly in a Stokes-Adams attack; the others, of coronary thrombosis or congestive heart failure.[7]

This hypertensive, arteriosclerotic patient succumbed to a typical cerebral episode, although no gross lesion could be demonstrated in the brain, post mortem. There was no evidence that epinephrine had caused a rupture of a cerebral vessel. The final course did not suggest any of the three forms of cardiac death. She apparently had been completely relieved of Stokes-Adams attacks for seven days prior to death.

SUMMARY

1. A case of Stokes-Adams syndrome has been presented which demonstrates graphically that the Stokes-Adams attack was due at different times to ventricular tachycardia, ventricular fibrillation, and ventricular asystole, either alone or in various combinations.

2. Interesting aspects of the physiology, pathology, and therapy in this case have been discussed.

Acknowledgement is made to Dr. Tom Brewer and Mrs. D. Semonds for their assistance in obtaining the electrocardiograms in this case.

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AN ANALYSIS OF CAUSES OF RIGHT AXIS DEVIATION BASED PARTLY ON ENDOCARDIAL POTENTIALS OF THE HYPERTROPHIED RIGHT VENTRICLE

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THE *electrophysiologic causes of right axis deviation* are clear cut. In the frontal plane of the body, delineated by Einthoven's triangle, deviation of the mean manifest potential to the right of a line drawn through the center of this plane, perpendicular to the horizontal side of the triangle, can only result when, during excitation of the ventricular muscle, the average potential of the left arm is at a lower level than the average potential of the right arm. Conceivably, this can occur in three ways when reference is made to a predetermined baseline of potential: the right arm may become more positive than the left; the left arm may become more negative than the right; or both processes may occur simultaneously in variable degree.

The anatomic causes of right axis deviation are not quite so definite, and may be multiple in any given instance. Some of the causes usually given are:

(1) Architecture of the Purkinje system: Individual differences in the arrangement of the ventricular conducting system have been used as an explanation of an abnormal axis, largely on the basis of the experiments of Rothberger and Winterberg[1] in dogs. When one considers the complicated embryonic development of the heart and its nervous system, the occurrence of anomalous or aplastic pathways, and hence, of abnormal electrical axes, is not hard to imagine, though not proven.

(2) Preponderance: Lewis[2] used the term preponderance to indicate that one or the other ventricle was hypertrophied. Although there was agreement in his experiments between the relative weights* of the two ventricles and the electrocardiographic findings, he was careful to point out[3] that in some instances of mitral stenosis, "preponderance, as estimated by weighing, is not discovered

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This study was aided in part by a grant from the New York Heart Association.

*The right ventricle and the left ventricle were separated from the septum, and the three resulting pieces weighed. A review of Lewis' paper[2] will show that his method was such as to include with each chamber, elements of muscle undoubtedly activated in a direction away from the cavity toward the septum. Such septal elements have an "electrical weight" opposed to that of the free walls.

in the expected ventricle. Neither are electrocardiographic signs of right hypertrophy discovered in all instances of mitral stenosis." Herrmann and Wilson[4] corroborated these findings in general, and presented evidence that the form of the ventricular complex and the relative weights of the two ventricles were closely inter-related only when there was considerable hypertrophy of the heart.

For the sake of completeness, the term preponderance may be expanded to include another situation. It is conceivable that sufficient muscle may undergo necrosis in the left ventricle and in the septum to cause preponderance of the right ventricle and right deviation of the electrical axis.[5] In a sense, this would result in a relative hypertrophy of the right side as a result of "atrophy" of the left side; the heart's center of gravity would be shifted to the right.

(3) Position of the heart: That the lie of the heart in the chest is important in determining the electrical axis was recognized long ago by Einthoven and associates,[6] Pardee,[7] Cohn,[8] Lewis,[3] and by Herrmann and Wilson.[4] More recently, it has become quite clear from a study of extremity potentials* that when the heart lies vertically in the chest the potential of the left arm may be negative, presumably because the origin of this extremity is then opposite the basal orifices of the heart.[9] If, as sometimes happens, the left arm is more negative on the average than the right, the standard leads will display an angle alpha in excess of +90°. Einthoven and associates[6] knew that the position responsible for such an electrocardiogram was the result of clockwise rotation of the heart not only about an anteroposterior axis, but also about a vertical axis.

The importance of position of the heart in the thorax, even when enlarged, in relation to the electrocardiographic findings was emphasized by Cohn.[8] Recent observations bear out his thesis. With regard to precordial leads, it is well known that a late RS or intrinsicoid[14] deflection, usually ascribed to a thickened underlying ventricular wall, is encountered in leads from the right side of the precordium in less than one-third of the patients with right ventricular hypertrophy secondary to mitral stenosis.†[15] Possibly a higher percentage, but by

*In recent years, the term "unipolar leads" has been applied to these records, and clinicians have come to use the term "unipolar" only in relation to these leads. Actually, the term "unipolar" in electrocardiography was first used by Groedel.[10] In its broader sense, it means that a lead has been made in such a way that the potential variations of the exploring (near) electrode are very much greater than the potential variations of the indifferent (distant) electrode. More specifically, it has come to mean a lead in which the zero-potential electrode of Wilson and associates has been used.[11] In a sense it is a misnomer, for no lead can be strictly unipolar even when the indifferent electrode is known to be at zero potential. But aside from this, a unipolar lead, as long as one electrode is nearer the source of potential than the other, may be obtained from any point on the body. Thus, we may speak of unipolar extremity leads (V_R, V_L, and V_F), unipolar precordial leads, unipolar esophageal leads, and unipolar intracardiac leads. For the last fourteen years all unipolar records have been made in this laboratory with the electrode of Wilson, Macleod, and Barker.[11] Augmentation[12] is occasionally used when recording extremity potentials, but the electrode described by Goldberger[12] is not used because, at times, records made with it display considerable variation from records similarly made with the electrode of Wilson and associates.[14]

†It has heretofore been believed[16] that the beginning of the intrinsic deflection or peak of R wave in direct leads marks the time of arrival of excitation under the exploring electrode. The experiments of Cole and Curtis[17,18] would seem to indicate that the end, rather than the beginning, of this deflection represents the occurrence of complete activity in underlying muscle. In semidirect (precordial) leads, the problem is complicated in proportion to the size of the variables defined by Poisson's integral,[19] and an intrinsic deflection as such is sometimes difficult to recognize. This more often is true of its termination than of its origin. For this reason, the term "intrinsicoid" is applied to the RS deflection in precordial

no means all of such deflections are late, particularly in Lead V_1, in congenital heart disease with right ventricular hypertrophy and in advanced chronic cor pulmonale. Another interesting feature of these records is that the R wave, when late, is usually later than a similar, smaller deflection recorded from the left side of the precordium, and is sometimes preceded by a Q wave. Assuming that thickness of the wall determines lateness of the intrinsicoid deflection, the clinical observations are not in accord with the pathologic, for in acquired heart disease a free right ventricular wall thicker than the left is almost never seen. Even in congenital heart disease it is not usual, except in the rare defect of uncomplicated pulmonary or infundibular stenosis.* Further, if the deflection were the result of right ventricular hypertrophy one would expect to see, more often, intermediate values which depend upon the extent of the hypertrophy. The occurrence of a small R wave and a deep S wave, and an absence of Q wave, in leads from the left side of the thorax in some of these cases is unexplained.

These data raise several questions: Is the late arrival of excitation on the right side of the thorax in the patients under consideration really caused by right ventricular hypertrophy, or does position of the heart in some way determine it? As a corollary, not particularly related to position of the heart, one might ask whether hypertrophy alone, in the case of the right ventricle, gives rise to a late large R or R′ in semidirect leads which are beyond a reasonable doubt in the electrical field of this chamber, or are other factors, such as partial defects in conduction on the right, responsible for it? To be answered also are the influence of left ventricular excitation on electrical events recorded over the right ventricle, and of the size as opposed to the thickness and weight of the right ventricle, in determining the occurrence of the deflection in question.

(4) Intraventricular block with normal QRS interval: There are electrocardiograms which display a late intrinsicoid deflection in one or several leads from the right side of the precordium with a QRS interval of less than 0.1 second.[20] These electrocardiograms may or may not display right axis deviation in the standard leads, and the patient may or may not show clinical or other evidence of cardiac disease. It is suspected that the curves obtained probably result from a partial defect in conduction on the right side. Further reference to this anatomic cause of right axis deviation will be made in a discussion of the last case to be presented.

SIMILARITY OF STANDARD LEADS WHEN RIGHT AXIS DEVIATION IS CAUSED BY DISSIMILAR ANATOMIC DEFECTS

In Fig. 1 are shown three standard electrocardiograms with characteristics in common. They differ principally in voltage and by the presence of a small

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leads as first used by Macleod, Wilson, and Barker[14] who, in introducing this term, undoubtedly had in mind the differences in this deflection as compared to the analogous one in direct leads.

Because of the practical difficulties involved in measuring the end of the intrinsicoid deflection, we have continued to use the beginning as a standard reference point. Whenever possible, a measurement of the size and duration of the potential developed across the subjacent wall has been made from the peak of Q or beginning of R when Q is absent, to the peak of S or the end of R when S is absent.

As will be seen it is particularly difficult to tell when the endocardium of the subjacent right ventricle has been excited.

*Of twenty cases found in the literature, sixteen showed a right ventricle thicker than the left.

R wave in Lead I of Patient C. Other features, such as a large QS or S in Lead I, and notched or slurred R waves and absence of S waves in Leads II and III, are similar. Also comparable are the T waves which have a direction opposite to the principal QRS deflections. All three patients were taking digitalis. The anatomic findings in each case were as follows:

Patient

A Mitral stenosis, mitral insufficiency, and questionable aortic insufficiency, with massive left atrium, determined clinically

B Extensive myocardial infarction, confirmed at necropsy

C Chronic cor pulmonale secondary to pulmonary emphysema, confirmed at necropsy

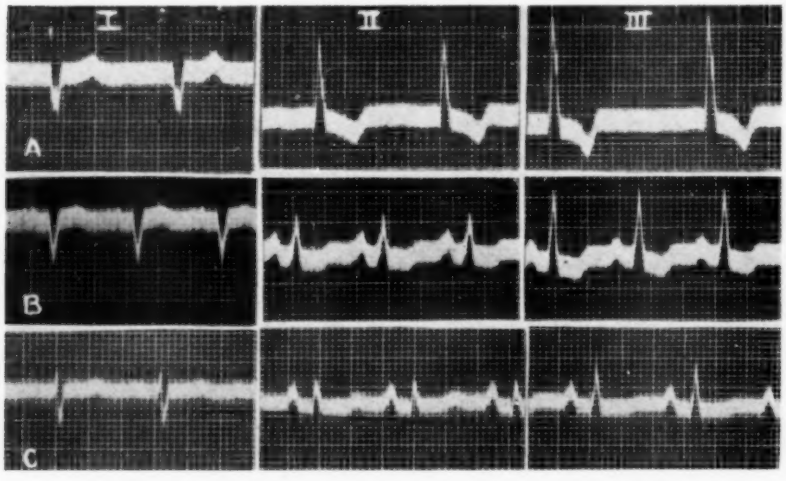

Fig 1.—Standard electrocardiograms (Leads I, II, and III) of Patients A, B, and C. Patient A was a 56-year-old white woman with rheumatic mitral stenosis and insufficiency, and probably aortic insufficiency. Patient B was a 42-year-old Negro with myocardial infarction. Patient C was a 42-year-old Negro with chronic cor pulmonale secondary to pulmonary emphysema. All three patients were in heart failure and were taking digitalis at the time the records were made. The diagnoses of Patients B and C were corroborated at necropsy.

The point illustrated is that widely different anatomic diseases can give very similar electrocardiograms. This, of course, is not new. But a more detailed electrocardiographic study of patients similar to these will demonstrate that deviation of the electrical axis in these three patients was caused by three distinct mechanisms, even though all might be spoken of as showing "right ventricular preponderance."

Studies on Patient B will be considered before the other two.

Right Axis Deviation With Infarction of the Left Ventricle.—Patient B showed an electrocardiographic pattern in standard leads which we have encountered in twenty-three patients in a random search. In fifteen of these, the extremity and six precordial potentials were recorded using the indifferent electrode of Wilson and associates;[11] in five, the hearts were available for section by the method of Kossmann and de la Chapelle.[21]

From the special leads of this patient (Fig. 2), the cause of the right axis deviation was easily ascertained. The right arm (V_R) was almost at zero potential instead of the usual negative, and the left arm (V_L) was distinctly negative. Precordial Lead V_5 simulated Lead V_L. This suggested that both were semidirect leads from the cavity of the left ventricle.

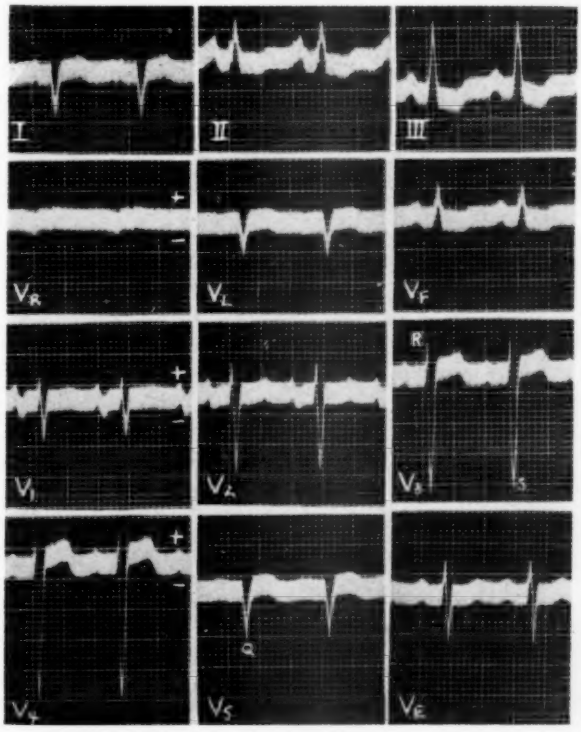

Fig. 2.—Patient B, myocardial infarction. Standard leads (I, II, and III) and extremity potentials (V_R, V_L, V_F) were recorded at normal string sensitivity (1 mv.= 1 cm.); the precordial potentials (V_1 V_2, V_3, V_4, V_5, V_E) were recorded at half-normal string sensitivity (1 mv. = 0.5 cm.). Leads V_1 to V_5 were made at the standard precordial points; Lead V_E was recorded from the tip of the ensiform cartilage. The extremity and precordial leads were made with the indifferent electrode described by Wilson, Macleod, and Barker.[11] Time lines occur every 0.04 second.

The negativity and similarity of QRS in Leads I, V_L, and V_5, and the low potential of QRS in Lead V_R, are to be noted.

At necropsy (Fig. 3), five days after the curves were recorded, there was found an extensive healed infarct extending from the apex for more than 6.0 cm. toward the base. Its circumferential and transmural extent was relatively less as it approached the base. At the apex the entire septum was involved, but toward the base the lesion in this structure was limited to its anterior half. In most places its entire thickness was involved, although small islands of muscle were preserved as was a subendocardial layer.[22] There was extensive mural thrombosis, especially at the apex, and the anterior wall close to the septum bulged slightly. The right ventricle was not involved. The infarct

resulted from thrombotic occlusion of the anterior descending branch of the left coronary artery. Although the lesion was extensive, it was clear that the remaining left ventricular muscle was in excess of right ventricular muscle. However, actual weights were not determined.

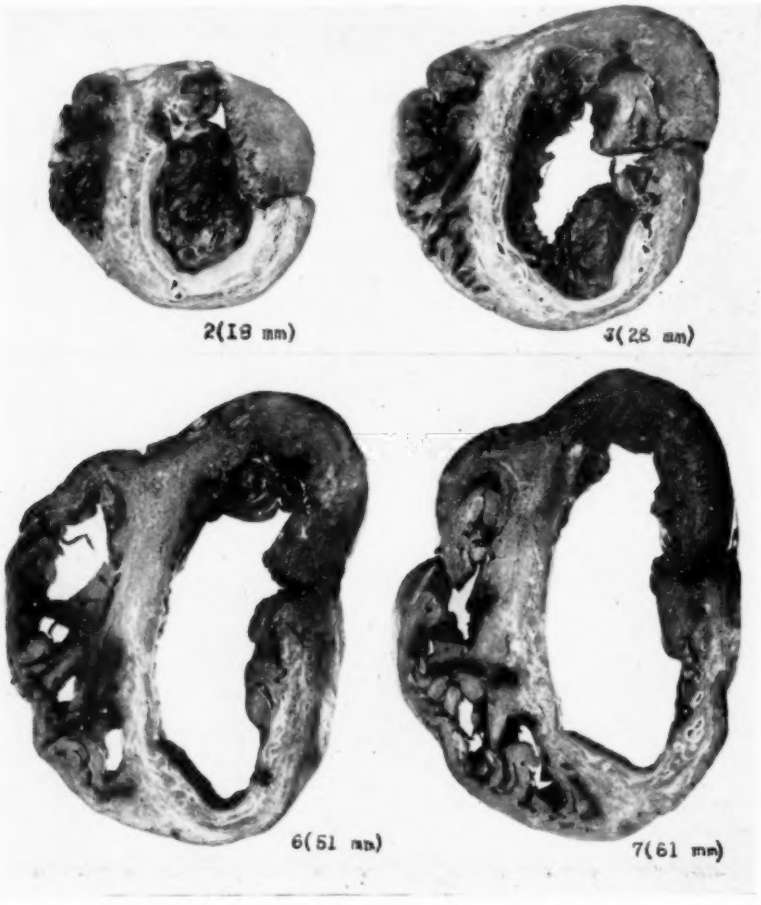

Fig. 3.—Patient B. Transverse sections 2, 3, 6, and 7 of the heart are shown. The basal side of each section is visible, with the anterior wall below and the left ventricle on the observer's right. The figures in parentheses indicate the level from the apex of the heart in millimeters.

Healed infarction is visible as the lighter areas in the septum, and in the anterior and lateral walls of the ventricles, mottled with small islands of remaining muscle. Thinning of these structures, mural thrombosis on the left, and slight bulging (aneurysm) anteriorly can be seen. The interlacement of trabeculae which make up the relatively normal right ventricular free wall are to be noted for later reference.

From the electrocardiograms of this and other patients in the series, it was evident that the right axis deviation was not due to a shift of the center of gravity of the heart, but rather was the result of the infarct being oriented with respect to the left arm. Any change in potential of the right arm from the normal probably resulted from the loss of left apical components directed downward,

which presumably contributed to its negativity before infarction occurred. The pattern displayed in the standard leads might be expected in a hypersthenic individual with a heart rotated in a counterclockwise manner in greater degree around its anteroposterior than around its long axis.

It was concluded from the group studied that preponderance of the right ventricle as a result of extensive necrosis of the left ventricle was a theoretical concept which probably does not occur.

Right Axis Deviation With Mitral Stenosis.—The teleroentgenogram (Fig. 4) of Patient A, who clinically was a case of rheumatic mitral stenosis and insuf-

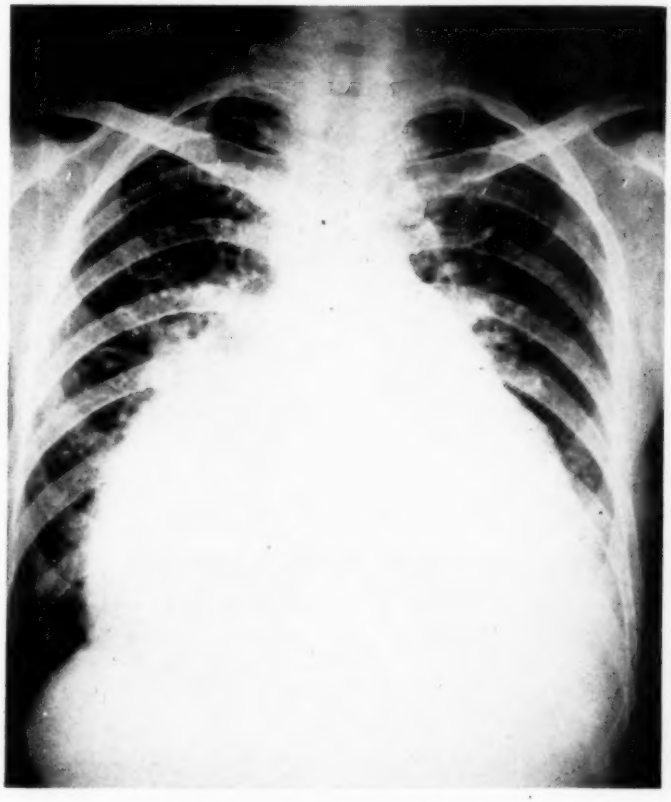

Fig. 4.—Patient A, rheumatic mitral stenosis, mitral insufficiency, and probable aortic insufficiency. Teleroentgenogram made within a short time of the electrocardiograms shown in Fig. 1. The massive size of the heart, filling of the cardiovascular angle on the left, and shadow of the left atrium on the right are the points of interest.

ficiency and possibly aortic insufficiency, showed a greatly enlarged heart of globular shape and displayed a shadow of a huge left atrium on the right border.

The extremity potentials (Fig. 5) revealed that the right axis deviation was the result of the left arm being more negative than the right, although both extremities were negative. The lead from the left leg was similar to leads from

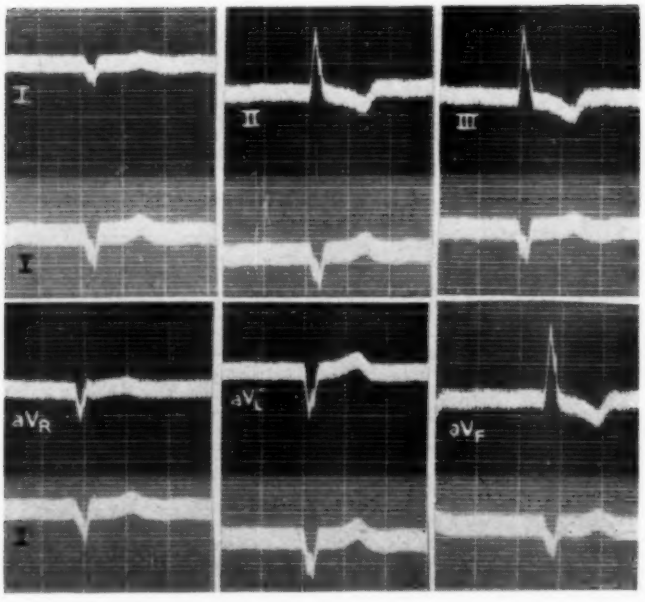

Fig. 5.—Patient A. Standard leads (I, II, and III) and augmented extremity potentials (aV_R, aV_L, aV_F) recorded simultaneously with Lead I, all at normal sensitivity of the string. The cause for right axis deviation is obvious from the greater negativity of the left arm (V_L) than the right (V_R) during inscription of QRS. The Q and late R in Lead V_F, and the similarity of this lead to Leads II and III are caused by the effects of the dependent left ventricle on the left leg. Time lines occur every 0.2 second.

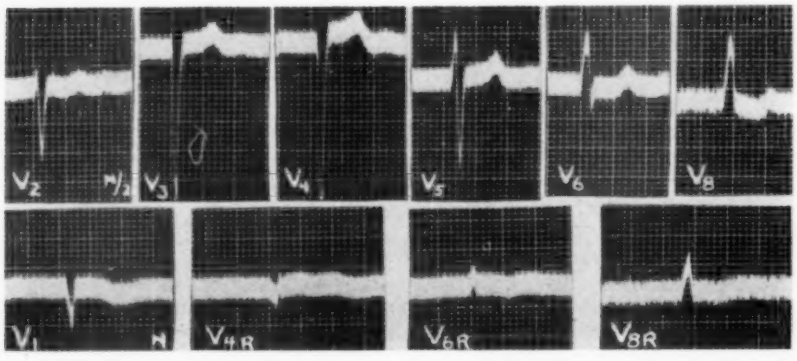

Fig. 6.—Patient A. Precordial potentials V_1 to V_6 were from the usual thoracic points. Lead V_8 was made with the exploring electrode in the left midscapular line at the same horizontal level as chest point 4. Leads V_{4R}, V_{6R}, and V_{8R} were recorded from the right side of the thorax, the arabic subscript indicating the position of the electrode as on the left side of the precordium. The records in the upper part of the figure were made with the string at half-normal, those in the lower part at normal sensitivity. Time lines occur every 0.04 second.

The small R wave in leads from the right side of the thorax, and its absence in Lead V_4, are to be noted. In Lead V_5 the R wave is "transitional."

the far left side of the precordium, indicating a vertical electrical position of the heart.[23] On investigating the precordial leads (Fig. 6), it was observed that a late R wave was not to be found on the right side of the precordium (Leads V_1 to V_5), as might be expected if such a deflection was caused by right ventricular hypertrophy. Actually, the R was quite small in these leads and even absent in Lead V_4, possibly due to a high position of the electrode on the chest. A late R wave, such as is usually obtained over the left ventricle, was recorded only when the exploring electrode was in the left midaxillary line (Lead V_6). Further, a similar late deflection was encountered with continued exploration of the back as far around to the right as the midaxillary line (Lead V_{6R}). Only when a lead from the right midclavicular line was made (Lead V_{4R}) did the curve obtained again resemble those found at other points on the front of the precordium.

With the anatomic knowledge that a large right ventricle makes up the greater part or all of the anterior surface of the heart, these electrocardiographic findings suggest that the anterior chest wall between the axillary lines was principally in the electrical field of the right ventricle and that the posterior chest wall between these lines was in the field of the left ventricle. Comparable lines of transition in a normal subject are on the average between the midclavicular line and the left sternal edge anteriorly[9] and, though quite variable, usually in the region of the dorsal spine posteriorly. This would mean that in Patient B considerable rotation of the heart in a clockwise manner around its long axis had occurred. To be noted particularly is that, although this right ventricle was distinctly hypertrophied (by inference and from x-ray findings), the R wave in its electrical field was early and small. It has been customary to ascribe such a finding to concomitant extensive hypertrophy of the left ventricle. Some enlargement of this chamber certainly existed but, as will be seen, it was probably not the factor responsible for the small R wave in leads from the front of the thorax.

To investigate the matter further, endocardial electrocardiograms were recorded in several patients after introduction of an electrode into the right atrium and right ventricle by way of an antecubital vein. The methods will be detailed elsewhere.[24]

In a normal subject with a vertical heart, the electrode at Points 1 and 2 as shown on the x-ray film (Fig. 7) was in the right atrium. At the remaining points (3 to 7), it was in the right ventricle. The location of the electrode when Lead V_3 was recorded from the chest is shown for comparison.

The standard and extremity leads, precordial Leads V_1, V_2, and V_5, and an intracardiac lead with the electrode in the right ventricle at Point 3, showed the following points of importance (Fig. 8): (1) Lead aV_R simulated Lead V_{RV3} (cavity of the right ventricle). (2) Leads V_1 and V_2 were similar to the intraventricular lead, although the R was a little taller in Lead V_2. The R waves and the S waves were a little later in the chest leads than in the cavity leads. (3) The intraventricular lead began with an R wave which was presumably the result of early activation of the left side of the interventricular septum. (4) The

T wave was negative with the electrode in the cavity, and positive with the electrode on the precordium.

Most noteworthy is that the R wave in a lead from the right ventricular cavity was slightly earlier than an R wave recorded from the right side of the precordium. Further, in Lead V_2 this deflection had two peaks. This and other

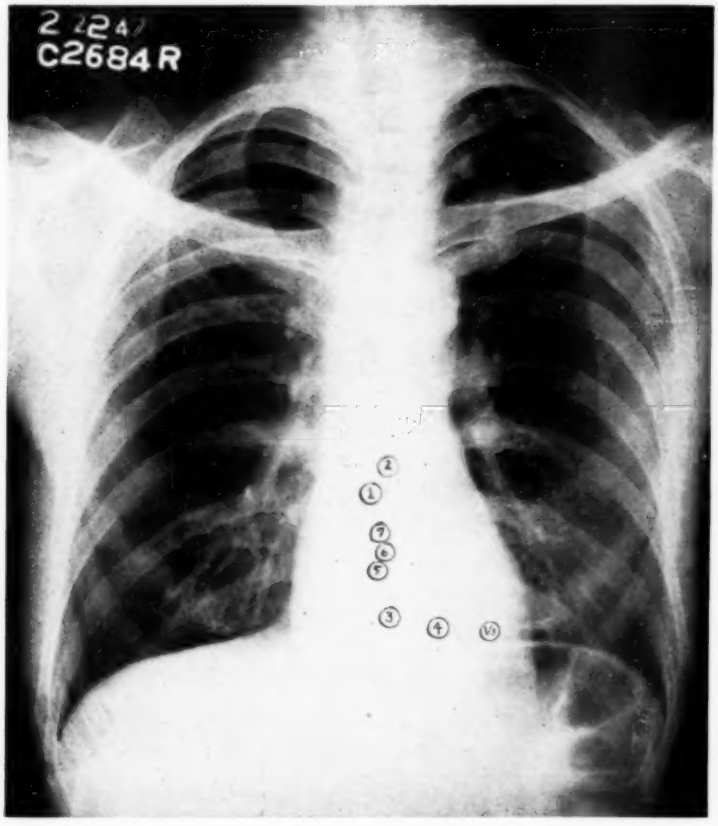

Fig. 7.—X-ray film of a patient with a normal heart showing various locations of an intracardiac electrode as projected on the thoracic surface by the central ray of the fluoroscope. At Points 1 and 2 it was in the right atrium; at Points 3 to 7 it was in the right ventricle. The location of Lead V_3 on the chest is shown for comparison.

This and subsequent similar x-ray films were made by putting a small metal marker on the chest directly over the intracardiac electrode during the catheterization. A teleroentgenogram was made immediately after completion of the electrocardiographic studies with the subject recumbent, as during the electrocardiographic studies, and again standing. Differences between the two were slight in this patient. The teleroentgenogram shown was made with the patient standing.

available data[24] suggest that this deflection has a dual origin in a precordial lead from the right side: first, it is caused by early excitation of the left side of the interventricular septum; and second, by passage of the action current through the free wall of the right ventricle. Any differences in the R wave of intracardiac

and extracardiac leads should be due to components contributed by the free wall of the right ventricle.*

In this and in other normal subjects studied, the amount contributed to QRS by the free wall was small. At least two explanations can be given: (1) the voltage developed across the free wall of the right ventricle is in truth small; and (2) the voltage developed across the free wall is slower than the simultaneous development of negativity of the cavity. One reason for believing the first to be correct will be discussed later.

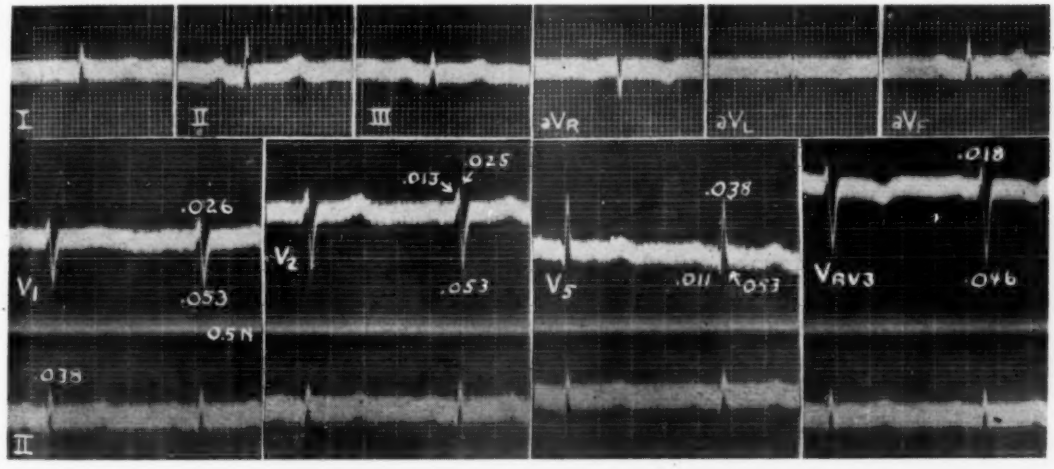

Fig. 8.—Patient with normal heart whose x-ray film is shown in Fig. 7. Leads I, II, III, aV_R, aV_L, and aV_F were recorded at normal sensitivity. Leads V_1, V_2, V_5, and V_{RV3} (right ventricular cavity with electrode at Point 3, Fig. 7) were recorded at half-normal sensitivity simultaneously with standard Lead II at slightly less than normal sensitivity of the string. The figures on the curves represent the time in seconds of the deflections over which they are written with reference to the beginning of QRS in Lead II. The time lines in the upper row occur every 0.04 second; in the lower two, every 0.2 second. To be noted are the similarity of Leads V_1, V_2, and V_{RV3} except for the direction of the T wave.

To return to the problem at hand, the question that arises next is how much does the free wall of the hypertrophied right ventricle in mitral stenosis contribute to the R wave? In this study another patient (W. F.) with rheumatic mitral stenosis, mitral insufficiency, and auricular fibrillation was used. The heart on x-ray study (Fig. 9) showed the characteristic shape, with prominence of the pulmonary artery or its left branch[25] in the middle arc. The left atrium was enlarged posteriorly. The standard leads (Fig. 10) showed an angle alpha of approximately $+60°$. The mean potential of the left arm was approximately zero, the electrical position was semivertical and hence QRS was upright in Lead I. Despite good clinical evidence of right ventricular hypertrophy, there were no R waves which were late or large in leads from the right

*Size of the R wave is not a reliable measure of the thickness of the underlying ventricular wall. Time of the deflection is perhaps more so, and most reliable of all is the size of the RS deflection, which in direct leads is a measure of the total electromotive force developed across the wall from endocardium to epicardium. But even this measurement is unreliable in indirect leads where the effect of surrounding conducting tissues, of the contralateral ventricle, and of perhaps other variables are unknown.

side of the precordium (Fig. 10, Leads V_{4R} to V_4). A small Q and late R were encountered in Lead V_5, and similar curves were obtained in leads from the left chest and back as far over to the right as the midscapular line. Beyond this, on the right the curves displayed all downward direction of QRS similar to that shown in Lead V_{4R}. The small size of R in curves obtained from the front of the thorax and its absence in Lead V_3 were similar to the findings in Patient A. Also of interest was the late small positive deflection in Lead V_2, which possibly arose in the pulmonary conus.[26]

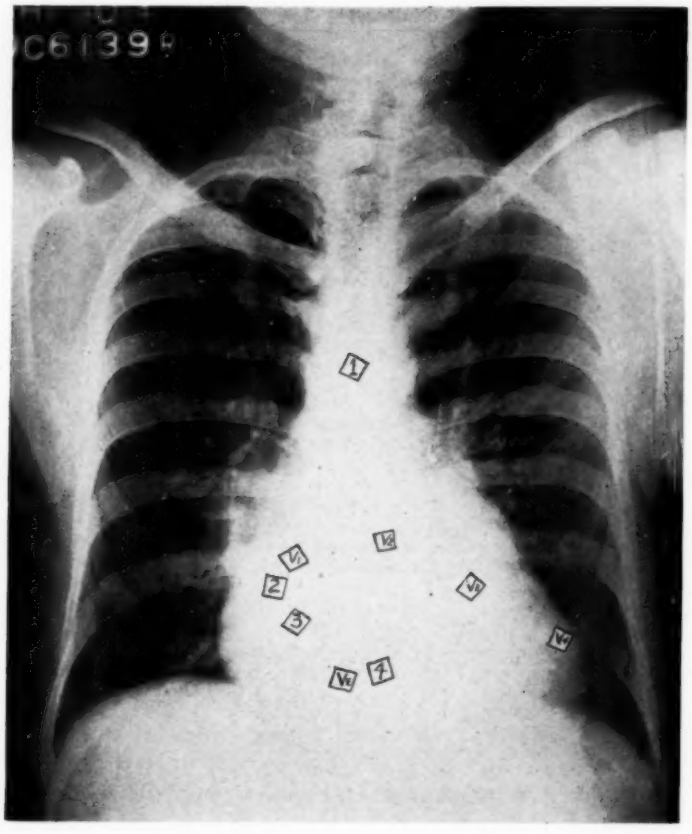

Fig. 9.—Patient W. F., rheumatic mitral stenosis and insufficiency. Teleroentgenogram made just after cardiac catheterization. Numbers on the heart shadow have the same significance as in Fig. 7. The patient was a 42-year-old white man with auricular fibrillation but not in heart failure. The characteristic shape of the heart is to be noted. On fluoroscopy there was marked enlargement of the pulmonary conus and left atrium, with some calcification in the wall of the latter. The left ventricle showed some enlargement posteriorly.

Potentials were obtained from both the right atrial and right ventricular cavities. While the electrode was in the inferior part of the right ventricle (Point 4 in Fig. 9), another electrode was placed directly over it on the precordium, and leads were recorded simultaneously with two string galvanometers (Fig. 11).

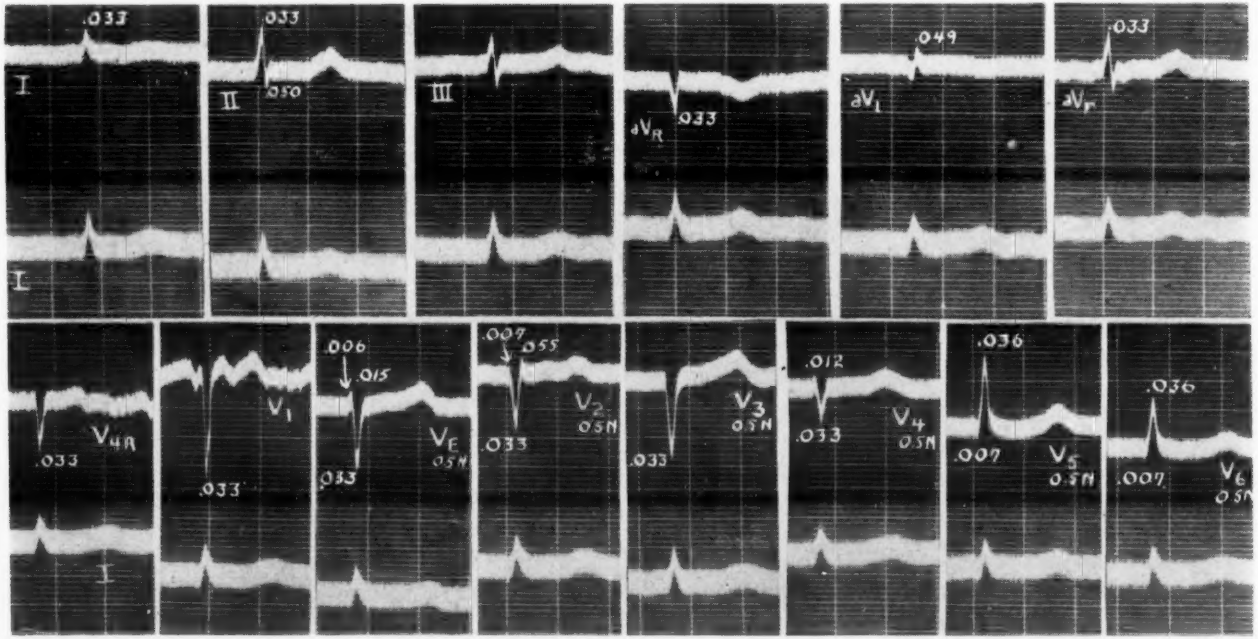

Fig. 10.—Patient W. F. Standard leads (I, II, and III), augmented extremity potentials (aV_R, aV_L, aV_F), and precordial leads (V_{4R}, V_1, V_E, V_2, V_3, V_4, V_5, V_6) recorded simultaneously with standard Lead I. Symbols and figures have the same significance as in previous illustrations. Leads V_7, V_8, and V_{8R} (not shown) were similar to Lead V_6. Lead V_{6R} (not shown) was similar to Lead V_{4R}. All leads in the upper row, and Leads V_{4R} and V_1 in the lower row, were recorded at normal sensitivity of the string; others at half-normal. Time lines occur every 0.2 second.

Both records were made with string sensitivity identical (0.6 normal). Quantitative differences were limited to a slightly smaller R wave and an inverted T wave in the lead from the cavity. Compared with the beginning of QRS in Lead I, the peak of R in the cavity lead was 0.004 second later, and the two peaks of R in the precordial lead were 0.006 and 0.015 second later, respectively. The opposite direction of the T wave in the cavity and precordial leads was probably caused, as in normal subjects,[24] by a gradient in the duration of the excited state across the free wall of the right ventricle such that activity was of longer duration on the endocardial surface.

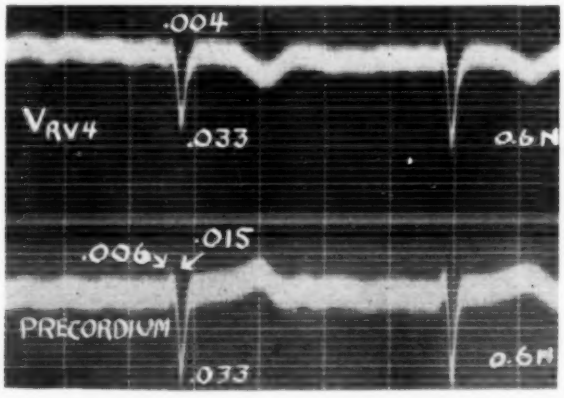

Fig. 11.—Patient W. F. Simultaneous records at identical string sensitivities (0.6 N) from a point inside the right ventricle ("V_{RV4}," upper string, electrode located at Point 4, Fig. 9), and from a precordial point directly over it ("Precordium," lower string). Figures indicate time in seconds between the deflection concerned and the beginning of QRS in Lead I.

To be noted are: similarity of the leads; the double peak of R in the precordial lead; and the opposite direction of the T waves.

It might be assumed that the contribution of the free right ventricular wall to QRS was small, and the R wave of the precordial lead not too different from the R wave of the cavity lead by virtue of dilatation. Although the patient was receiving digitalis, he displayed no evidence of congestive heart failure at the time the records were made. Dilatation of the right ventricle was not present.

It would appear from these data that the lateral wall of the right ventricle contributes little to the extrinsicoid deflection or R wave in leads from the right side of the precordium, and that this statement is true when the right ventricular wall is thickened as a result of mitral valvular disease with stenosis. Further, clockwise rotation of the heart about its long axis, as illustrated in Patients A and W. F., is apparently not extensive when there is mitral stenosis even when right ventricular hypertrophy is considerable, as in Patient A. A possible explanation is that the concomitantly enlarged left atrium prevents such rotation to any extreme degree.

Right Axis Deviation in Chronic Cor Pulmonale.—Patient C showed chest leads which differed from those seen in the records of the patients with mitral

stenosis. A lead from the right sternal edge, though of very low voltage, displayed a Q, a late R, and an inverted T. In the only other precordial curve available, Lead V_5, there was a small R, deep S, and positive T. No other special leads were available on this patient before death. At necropsy, the right ventricle was abnormally thick but not thicker than the left, even though the R wave, measured from the beginning of QRS, was later on the right than on the left by approximately 0.01 second.

Another patient, A. K., with advanced chronic cor pulmonale, was available for detailed study. The standard leads (Fig. 12) displayed a deep S wave in Lead I; Leads II and III were low and bizarre. From the extremity potentials the electrical position of the heart was indeterminate because of the low, vibratory nature of Leads aV_L and aV_F.

Lead aV_R was similar to Lead V_1 (Fig. 13) and to all the leads recorded to the right of the midline as far around the back as the midscapular line (Lead V_{8R}, not shown). The intracavitary potential of the right atrium (not shown) had an identical contour.

Notable in the precordial leads which were recorded simultaneously with a lead from the cavity of the right ventricle (Fig. 13) were: their similarity to those of Patient C; the abrupt change in the curve as soon as the midline was crossed (Lead V_E, not shown, was similar to Lead V_1), although anatomic considerations would indicate that certainly precordial Points 2 and 3 and probably 4 were in the electrical field of the large right ventricle; and the small R wave and prominent S wave without a Q wave, such as are seen over the normal right ventricle, even in a lead as far to the left as Lead V_7 (which was similar to Lead V_6, Fig. 13). The peak of the R was earlier in Leads V_2, V_3, and V_4 than in Leads V_5 to V_7 (0.004 second and 0.025 second, respectively, measured from the beginning of QRS in Lead I). On the other hand, leads from the right side and back of the thorax (V_1, V_{4R}, V_{6R}, and V_{8R}) and from the cavity of the right atrium displayed a Q, a late large R, and an inverted T. In all these leads, with one exception which will be discussed, the peak of Q and the peak of R occurred, respectively, at an identical time; namely, 0.016 and 0.050 second after the beginning of QRS in Lead I.

When an electrode was placed on the precordium directly over the intracardiac electrode (Fig. 14) and leads were made simultaneously (Fig. 13, "V_{RV2}" above and "Precordium" below), the curves did not differ in general contour, although there were differences compared with the records of the case with mitral stenosis (Fig. 11) similarly made. The R wave in the endocardial lead consisted of three different peaks, only the first of which preceded the peak of R in the chest lead. Although the relative size of R and S was approximately the same in both records, the RS deflection measured approximately 18 millivolts in the cavity lead compared with 3.0 millivolts in the lead from the precordium. The S wave in the cavity lead preceded the initial peak of S in the chest lead by a small interval (0.005 second), but the second peak of S in the latter was 0.023 second later, and was simultaneous with the R wave in leads from the right side of the thorax. This indicates that the first peak of S resulted from the comple-

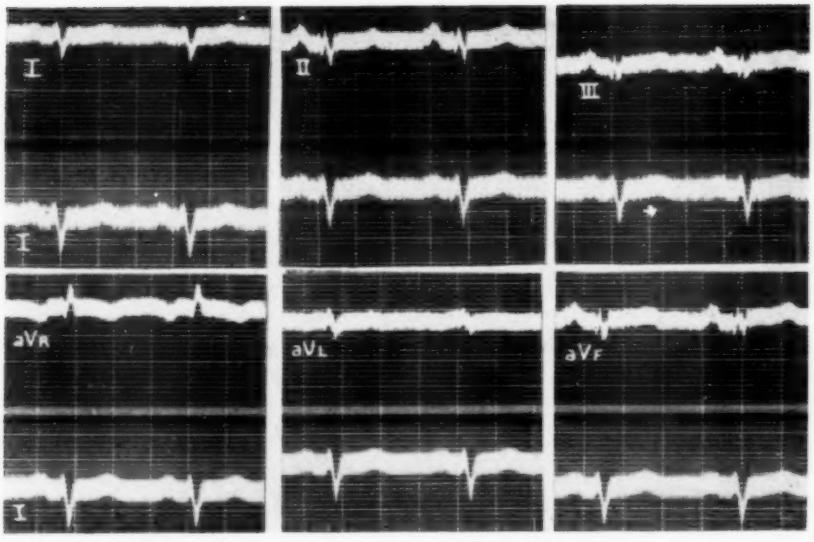

Fig. 12.—Patient A. K., a 57-year-old white man, who had been a coal miner in youth and who was regarded as having chronic cor pulmonale for five years before the electrocardiograms were recorded. He was taking digitalis. The standard leads (I, II, III) and augmented extremity leads (aV_R, aV_L, aV_F) were recorded simultaneously with Lead I. Time lines, 0.2 second.

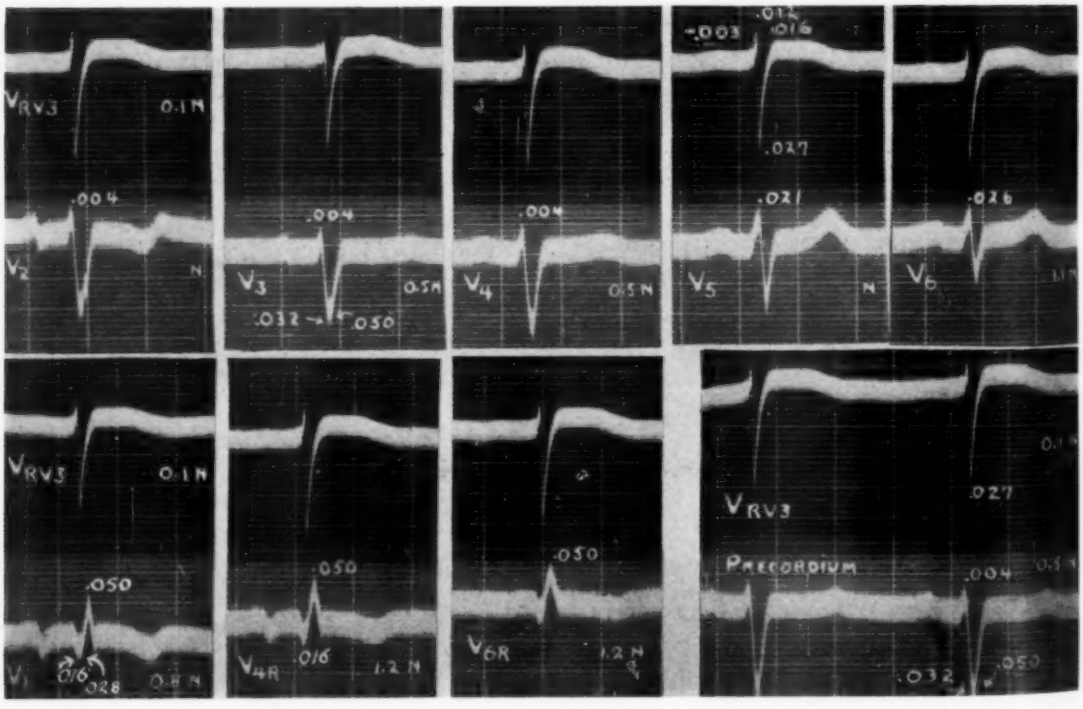

Fig. 13.—Patient A. K. Right intraventricular Lead V_{RV3} (upper string at 0.1 N sensitivity) from Point 3 in ventricle (see Fig. 14) recorded simultaneously with various precordial leads at varying string sensitivities as indicated. Leads V_E, V_{8R}, and a lead from within the right atrium (Point 5, Fig. 14) were similar to Lead V_{6R}. Figures indicate the time in seconds of the deflection concerned from the beginning of QRS in Lead I. The R wave of the intraventricular electrocardiogram shows three distinct peaks. In the lower right hand corner a lead from the ventricular cavity (V_{RV3}) was recorded with a lead (precordial) from a point on the chest directly over the intracardiac electrode. Time lines, 0.2 second.

tion of activity across the underlying ventricular wall while the second peak was a distant event, resulting from excitation reaching the epicardial surface of the contralateral ventricle. Since the precordial lead as taken was almost definitely in the electrical field of the right ventricle, the contralateral ventricle in this instance was the left ventricle.

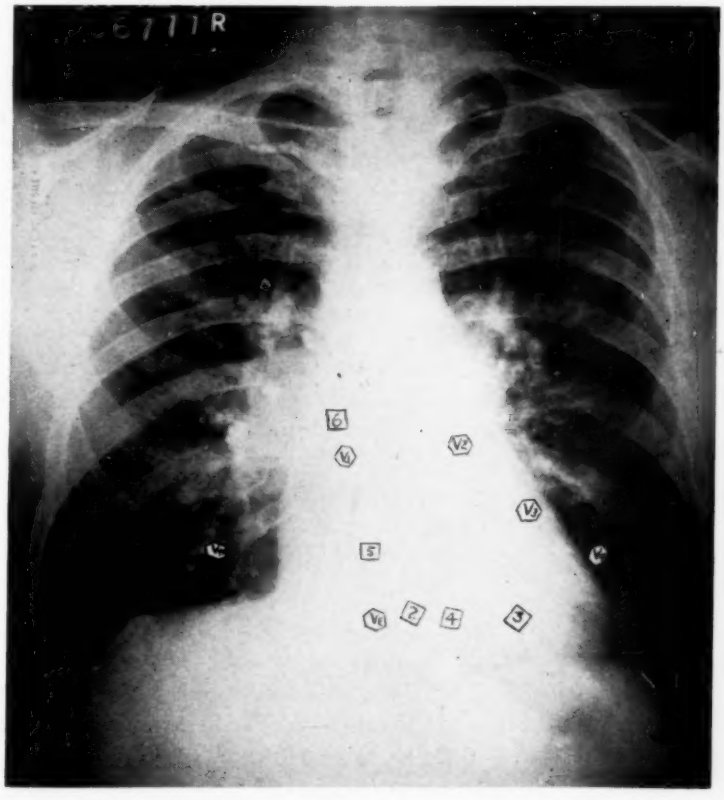

Fig. 14.—Patient A. K. Teleroentgenogram made with the patient standing, lead markers having been placed at points on the chest from which precordial leads were taken (hexagonal figures) and over the locations from which endocardial leads were made (square figures). To be noted are: the location of Point 3 at the apex of the right ventricle; the high location of Leads V_1 and V_2 as opposed to Lead V_E; and the location of Lead V_{ER} (just visible in lower left hand corner of figure). At Point 6, the intracardiac electrode was in the superior vena cava; at Point 5, it was in the right atrium; at the others, it was in the right ventricle.

The shape of the heart and the length of the thoracic cavity are to be noted.

These data, when interpreted in the light of what has been presented up to now, make it necessary to come to the following conclusions. The left ventricle, and not the thickened right ventricle, was responsible for the late intrinsicoid deflection encountered in leads from the right side of the thorax in this case of chronic cor pulmonale. It appears that there was extreme clockwise rotation of the heart around its long axis to an even greater degree than in the patients with mitral stenosis. The right ventricle was rotated far to the left, and a transi-

tional zone occurred over a wide area in the left axilla. The actual change from right ventricular to left ventricular electrical fields was posterior rather than in the left parasternal line anteriorly as in normal subjects. Further, the transition zone from left ventricle to right ventricle, instead of being posterior, was in the vicinity of the midsternum anteriorly.

At first glance this seems incredible from an anatomic point of view. Studies that have been made with angiography are not of much help because of the difficulty encountered in visualizing the left ventricle. Examination of a good heart model will show that it is entirely possible, particularly if, in addition to the clockwise rotation about the long axis of the heart viewed from the apex, there is also considerable similar rotation about an anteroposterior axis and transverse axis viewed from the left. It is believed that such unusual degrees of rotation can occur in chronic cor pulmonale because the voluminous lungs make it possible by greatly increasing the anteroposterior and long diameters of the thorax. Further, there is no great enlargement of the left atrium posteriorly, as in mitral stenosis, to interfere with rotation about the long axis.

It is probable that the left ventricular curve obtained in Lead V_1 was not the result of a direct relationship of the exploring electrode to the surface of the left ventricle, but rather was indirect through the intervening right atrium. It is surmised that this latter chamber which is enlarged in cor pulmonale, particularly if heart failure has occurred, may actually overlap the posterior basal part of the left ventricle. A point in support of this is that an intra-atrial lead in the case under consideration displayed a curve identical with that obtained from the right sternal edge.

It is probable that the peak of the Q wave in Lead V_1 was not created in the way that a Q wave usually is when an electrode is over the left ventricle. It was discovered that the last part of the Q was simultaneous with the peak of the S wave in the cavity of the right ventricle. It is possible, therefore, that it was created in part as a result of Lead V_1 being a semidirect lead from the cavity of the right ventricle by virtue of the electrode being close to the auriculoventricular orifice of this chamber. This explanation is plausible if the anatomic considerations given before are accepted. Further, in Lead V_{4R}, and in others to the right, the peak of Q was simultaneous with the peak of R in the cavity lead from the right ventricle, while its ascending limb was slurred at a time when the peak of S in the cavity lead was written. In these leads, then, only part of the Q wave was created in the manner described for Lead V_1.

If this explanation of the origin of the Q wave in Lead V_1 is correct, this deflection becomes unreliable as an index of beginning excitation of left ventricular endocardium subjacent to the electrode (see footnote, † p. 310). However, it may be reliable in other leads made at lower levels and more posteriorly on the right, in which the peak of Q was simultaneous with the peak of the R wave in the cavity leads (about 0.016 second from beginning of QRS in Lead I).

RIGHT AXIS DEVIATION IN TETRALOGY OF FALLOT

A patient, M. F., 11 years of age, with a clinical diagnosis of tetralogy of Fallot, was explored electrocardiographically, although cavity potentials were not recorded. The electrocardiograms (Fig. 15) showed the usual right axis deviation in the standard leads. The special leads were strikingly similar to those in the case of chronic cor pulmonale just presented (Patient A. K.). Of particular interest were: the Q and late R in Leads aV_R and aV_F, although the T wave was negative in the first and positive in the second; the similarity of Leads V_2 to V_8 (left midscapular line) with a relatively small R, except in Lead V_4, and a deep S; the similarity of all leads from the middle of the sternum to the right as far as the right midscapular line (Lead V_E to Lead V_{8R}), and the likeness of these to Leads aV_R and aV_F; and the abruptness of the change between Leads V_2 and V_E.

The x-ray films were not unusual, although an angiocardiogram* made in the left anterior oblique position showed a posterior left ventricle, free of contrast media; an aorta, pulmonary artery, and right ventricle filled as expected; and a persistent right aortic arch (Fig. 16). The considerable spaciousness of the retrocardiac space, and the right-sided aorta presumably facilitated clockwise rotation of the heart around its long axis.

The patient came to necropsy two days after the electrocardiograms were made following an unsuccessful surgical exploration. There was a tetralogy of Fallot with infundibular stenosis. The right ventricle ranged in thickness from 7 mm. at the apex to between 7 mm. and 10 mm. at the base. The conus just below the stenosis measured 6 mm. in thickness. The walls of the cavity, particularly in its apical four-fifths, were irregular, and were made up of thickened, closely packed trabeculae which, however, could easily be separated except at the base. The left ventricle was slightly thicker, and measured 11 mm. at the apex and 10 mm. at the base. Its endocardial surface, in contrast to that of the right ventricle, was relatively smooth throughout. Its wall was made up of solid muscle rather than of closely packed, interlaced and hypertrophied trabeculae.

Several facts stand out in this case. The free walls of the right and left ventricles were of almost the same thickness, yet the electrocardiograms displayed intrinsicoid deflections which appeared at widely different times on the two sides of the precordium (Fig. 15). Undoubtedly there were multiple causes for this, but one possible anatomic reason could hardly go unnoticed, namely, the different structure of the two chambers. If reference is made to Fig. 3, it will be seen that the right ventricular wall is made up of trabeculae which in places almost fill the cavity. The "wall" itself is made up of only the thinnest layer of what may be called "solid muscle," and this is probably even thinner in the distended living ventricle. No matter in which direction it is assumed that the trabeculae are stimulated, from the outside, from the center, or eccentrically, the total electrical effect of these trabeculae must be small.

*The authors are grateful to Dr. U. J. Roche for making this angiocardiogram with the help of the radiologists at Lenox Hill Hospital, New York, N. Y.

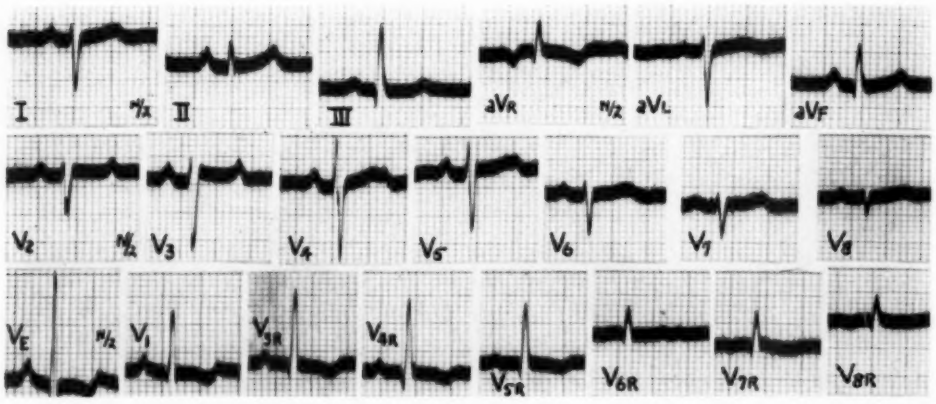

Fig. 15.—Patient M. F., with the tetralogy of Fallot. All leads were recorded at 0.5 N sensitivity of the oscillograph. Designation of leads is the same as in previous tracings. To be noted are similarity of leads in the second row to Lead aV_L and to each other, and the similarity of the curves in the lowest row to Leads aV_R and aV_L, and to each other.

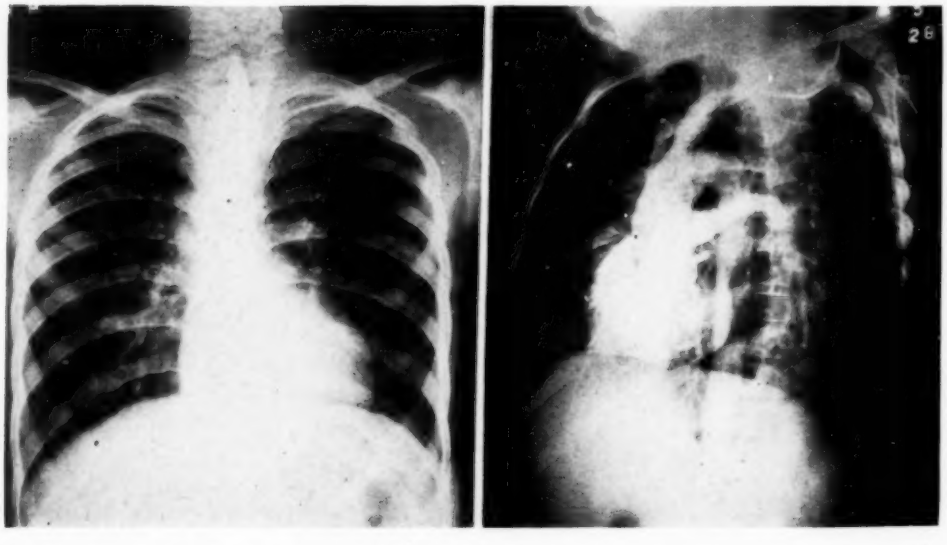

Fig. 16.—Patient M. F. Teleroentgenogram on left with barium in esophagus, and on the right an angiocardiogram made with the patient in the left anterior oblique position. In the latter, the contrast medium is in the right ventricle, in the aorta, and in the pulmonary artery. The aorta is on the right. To be noted is the considerable distance between the heart and the spine posteriorly.

When there is hypertrophy of the chamber, as in the present case, there is merely an exaggeration of this situation, perhaps with some increase in the "solid" wall especially of the base, but the total electrical effect is theoretically still small if intraventricular conduction is unimpaired.

RIGHT AXIS DEVIATION AS A RESULT OF INTRAVENTRICULAR BLOCK WHEN THE QRS INTERVAL IS WITHIN NORMAL LIMITS

The electrocardiograms of Patient J. R. are shown in Fig. 17. This 59-year-old patient had arteriosclerotic and pulmonic heart disease with a dilated pulmonary artery, and pulmonic valvular incompetence[39] whenever he was admitted to the hospital in heart failure. However, x-ray films showed a large left ventricle as well as a long pulmonary arc (Fig. 18). The lungs were emphysematous. At the time the electrocardiograms were recorded the patient was taking digitalis.

The curves differed in several important respects when compared with those of Patient A. K. (Figs. 12 and 13). Deviation of the electrical axis to the right was not so marked. In Lead aV_R, the Q wave preceding the late R was deeper. The small R in Lead aV_L was preceded by a minute Q wave. This lead was similar to leads obtained from the left side of the precordium (V_5 to V_7). The ventricular gradient in the frontal plane was further to the left, possibly in part attributable to digitalis. The QRS interval was 0.094 second.

The thoracic leads differed quite markedly (Fig. 17). Leads V_1 and V_2 displayed an initial R wave of small size which was followed by a small S and a late large positive deflection which was splintered, so that there was actually an R′ and R″. Contours in Leads V_{3R}, V_{4R}, and V_{5R} were similar except that R″ could not be identified. Farther to the right, the R could not be seen but the R′ (now really R) was late, though small, as far around as Lead V_{8R}. Continuing to the left, Leads V_8, V_7, V_6, and V_5 showed a different contour with an early R, and a broad but similar sized S wave. A small Q was present in Leads V_5, V_6, and V_7 which can be seen better, at least in Lead V_5, in Fig. 19.

In Leads V_3 and V_4 there were features simulating both dominant types of curves suggesting that these leads were from transitional zones.

It would appear that rotation, such as was present in the prior two instances, was not present in this case (Fig. 18). The small Q and rapid R in Leads V_4, V_5, and V_6 suggest that these deflections were part of the levocardiogram, and that the broad S was in some way caused by events on the right side, or at any rate by electrical forces proceeding away from the left side.

The potential of the right atrium during ventricular excitation consisted of an initial small positive deflection, a deep negative deflection, and a late broad positive deflection (R′) and an inverted T wave. The ventricular cavity (Figs. 19 and 20), explored at several levels, displayed deflections of the same nature throughout except when the electrode was against the endocardium so as to cause displacement of the S-T segment. The "average" potential consisted of an R wave, usually notched, and a deep S with several smaller notches on its descending limb (Fig. 19).

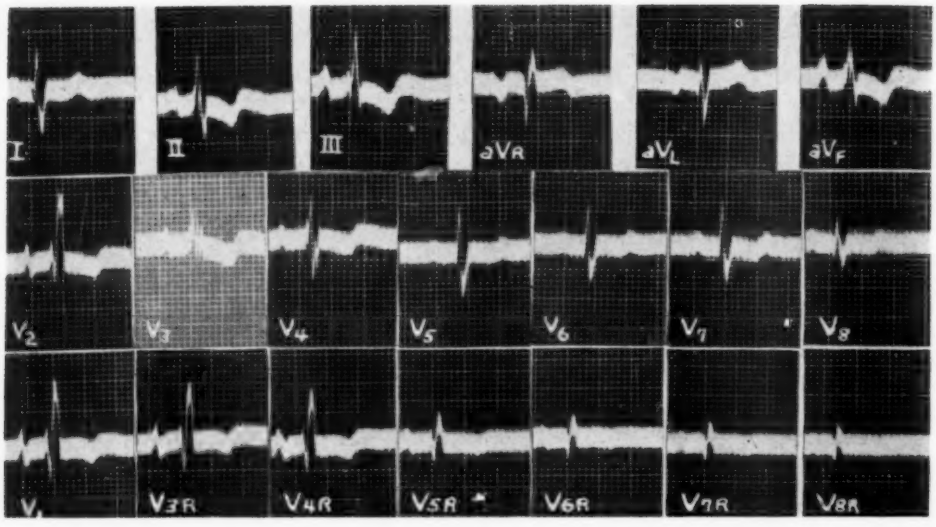

Fig. 17.—Patient J. R., arteriosclerotic and pulmonary heart disease with intraventricular block. In the standard, extremity, and precordial leads, symbols have the same meaning as in previous records. The precordial leads were recorded at 0.5 N sensitivity of the string. The QRS interval in the standard leads was 0.094 second. Time lines, 0.04 second.

To be noted are the R wave and splintered R′ in Leads V_1 and V_2; the absence of splintering of R′ in Lead V_{3R} and other leads farther to the right; the transitional nature of the ventricular complexes in Leads V_3 and V_4; and the small Q (barely perceptible, see Fig. 19) in Leads V_5 to V_8.

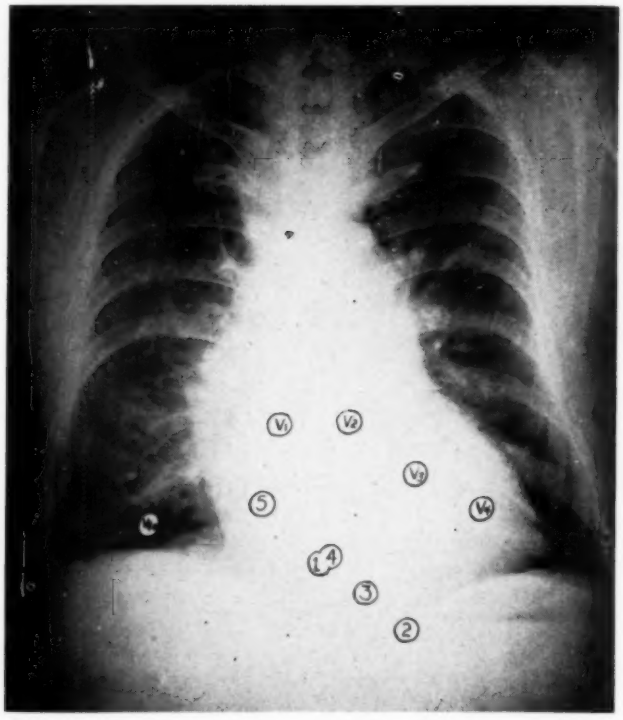

Fig. 18.—Patient J. R. Teleroentgenogram made with patient standing just after cardiac catheterization. Location of the points from which precordial leads were made are indicated by the usual symbols. Location of Lead V_{5R} can be seen at the extreme lower left. Arabic numerals in a circle indicate the location of the intracardiac electrode projected by the central ray of the fluoroscope onto the thoracic surface. At Point 5, the electrode was in the right atrium; at the other points (1 to 4), it was in the right ventricle.

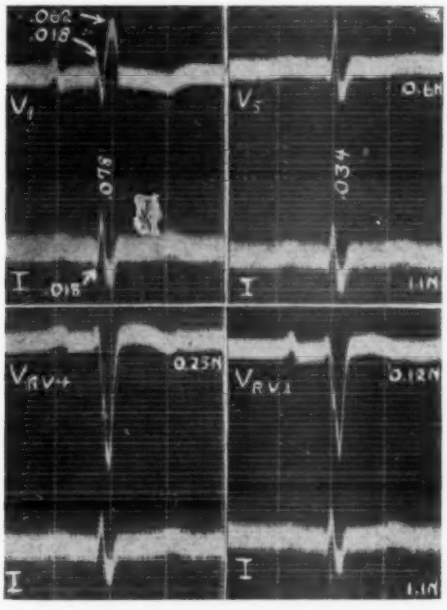

Fig. 19.—Patient J. R. On the left are Leads V_1 and V_{RV4} (right ventricular cavity at Point 4 Fig. 17), each recorded simultaneously with standard Lead I. The two sets of curves have been selected so that the time line marked vertically as 0.078 second (from beginning of QRS in Lead I) is approximately simultaneous in both. To be noted is the simultaneity of R″ in Lead V_1 with the last part of S in Lead I, and with the ascending limb of the S wave in the cavity lead. The R wave in Leads V_1 and V_{RV4}, and the Q wave in Lead I, are simultaneous. R′ in Lead V_1 is simultaneous with the first part of S_1 and with the peak of S in the cavity lead.

On the right are Leads V_5 and V_{RV1} (right ventricular cavity at Point 1, Fig. 17), each recorded simultaneously with Lead I. The two sets of curves were selected so that the time line marked vertically as 0.034 second (from beginning of QRS in Lead I) is approximately simultaneous in both. This demonstrates the simultaneity of R waves in Leads V_5 and I with the notch on the descending limb of the S wave in the cavity lead. String sensitivities were as noted. Time lines, 0.2 second.

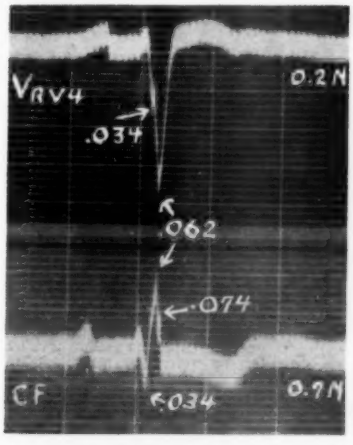

Fig. 20.—Patient J. R. A lead from the right ventricular cavity (V_{RV4}) was recorded simultaneously with a precordial lead; the exploring electrode of the latter was placed on the chest directly over the intracardiac lead, and the indifferent electrode on the left leg (CF). Figures indicate time of deflections with respect to the beginning of QRS in Lead I. Absence of positivity in the cavity, except initially, is noteworthy. Sensitivities of the strings were as noted. Time lines, 0.2 second.

The R wave in the lead from the ventricular cavity was simultaneous with the small R wave in Leads V_1 and V_2, and with the Q wave in Leads I, V_5, V_6, and V_7. The notch on the descending limb of the S wave of the intracardiac lead was simultaneous with the S in Leads V_1 and V_2, and with the R in Leads I, V_5, V_6, and V_7. R′ in Leads V_1 and V_2 was simultaneous with the peak of S in the cavity lead, but the second notch of R (R″) in Leads V_1 and V_2 occurred at a time when negativity of the right ventricular cavity was rapidly diminishing. Written simultaneously with R″ was the last peak of the S wave in Leads I, V_5, V_6, and V_7. These relationships are fairly easily seen in the curves of Fig. 19, where an attempt was made to align on the left the simultaneous events occurring with R″ of Lead V_1, and on the right the events occurring simultaneously with R in Lead V_5.

The origin of some of these relationships is quite clear; of others, quite obscure. It seems certain that the small R wave in leads from the right side of the sternum and from the right ventricular cavity, and the Q wave in leads from the far left side, as well as the Q wave in Lead I, resulted from early excitation of the left side of the interventricular septum. The simultaneity of the ascending limb of R in leads from the left and the initial part of the descending limb of S in the right ventricular lead strongly suggests that the latter event in the cavity was principally due to propagation of the impulse through the lateral wall of the left ventricle. Although this explanation is difficult to sustain on the basis of the laws governing currents in volume conductors, further credence is given to it by the fact that the peak of the R wave in Lead V_5 was simultaneous with the notch located approximately halfway down on the descending limb of the S wave found in the cavity lead (Fig. 19).

The peak of R′ in Lead V_1 was simultaneous with the peak of S in the lead from the cavity, which supports the belief that the electromotive force responsible for these deflections was the same, and that this force probably was acting across the wall of the right ventricle. Disturbing, of course, is the fact that this did not occur in other cases (W. F. and A. K.) with right ventricular hypertrophy. Further, and contrary to the theories thus far developed, is the fact that a longer time was required for the excitation to reach the epicardial surface of the right ventricle than of the left. This was calculated as follows: In Lead V_5 (Fig.19) the time was measured from the peak of Q (beginning excitation of endocardium nearest the exploring electrode) to the initial peak of S (taken as representing complete excitation of the underlying wall); in Lead V_1 a similar interval was measured from the peak of S (Fig. 17) to the small depression between R′ and R″. It is evident that failure of the last deflection to reach the baseline because of the ascent of R″ introduces an error in the direction of foreshortening. Nevertheless, the figure obtained from the left was 0.034 second and from the right 0.034 second, plus the error referred to. This would mean that the right ventricle was thicker than the left if the variables introduced by indirect leading are disregarded. This, as noted previously, is contrary to anatomic observations, and in this patient the left ventricle was enlarged as well as the right, making a conclusion that the right was thicker than the left even less likely. It is almost

certain that this deflection (peak of S to peak of R′ in Lead V_1) was caused by a delay in propagation of the impulse across the right ventricular wall. The exact mechanism involved is unknown, but the block was very probably distal to the right bundle branch. This statement is made because the cavity of the right ventricle was negative except in the early part of ventricular excitation. If the bundle branch was blocked and the septum was excited from left to right, one would expect the right ventricular cavity to be distinctly positive during some period of ventricular excitation[26,28,29] other than the initial period when positivity normally occurs.[24]

The R″ in Lead V_1 is interesting in that it occurred at a time when the negativity of the right ventricular cavity was decreasing rapidly (Figs. 19 and 20). It occurred very late in the QRS interval (0.074 second from the beginning of QRS in Lead I). The force responsible for R was of sufficient magnitude, however, to keep the left side of the precordium negative (last peak of S wave in Lead V_5). Therefore, it is not believed to have been caused by excitation of the pulmonary conus alone (as seen in dogs). There would seem to have been some considerable amount of muscle, probably around the entire base of the right ventricle, which was still being excited long after the action current had been extinguished across the remainder of the right ventricular wall. Reasons for saying this are that the base of a hypertrophied right ventricle, unlike the apex, is often thick and solid instead of trabecular. Further, in the present case, a set of precordial leads made one intercostal space below the conventional levels failed to display the R″, and in Lead V_2, made in the fifth intercostal space, it was actually replaced by a small S. This means that the force it represented was proceeding not only to the right but also upward.

SUMMARY

1. The physiologic and anatomic reasons for deviation of the electrical axis to the right are reviewed.

2. In certain patients with myocardial infarction, right axis deviation results when the infarct is so oriented that the left arm is in effect a semidirect lead from the cavity of the left ventricle, and is more negative during ventricular excitation than the right arm.

3. Considerations and data are presented which make it doubtful that the hypertrophied right ventricle, except in rare instances, can cause right axis deviation by itself. Rather, it appears to have its dominant effect on the electrocardiogram by changing the position of the heart in the thorax.

4. In certain diseases characterized by a large right ventricle and conditions in the thorax which favor rotation of the heart about its long axis, it is believed that extreme rotation of this organ with almost complete reversal of the electrical fields of the two ventricles in the thorax may occur.

5. When excitation of all the ventricular muscle requires less than 0.1 second, and right axis deviation is accompanied by a late R′ in leads from the right side of the precordium, the deviation and the deflection are probably caused

by a delay in propagation of excitation across the free wall of the right ventricle, this delay being distal to the bundle branch. Under such circumstances the R′ may be somewhat exaggerated in size and duration by late components contributed by the base of the right ventricle, particularly if it is hypertrophied.

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FLUOROCARDIOGRAPHY (ELECTROKYMOGRAPHY)*

I. Technical Aspects

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THE importance of obtaining accurate records of the pulsatory changes of the cardiac chambers and the large blood vessels is self-evident. Indirect recording, using sphygmography, phlebography, esophagocardiography, and cardiography, has been employed for this purpose, but all these methods have definite limitations and contain sources of error.

The roentgen ray permits direct visualization of cardiovascular silhouettes and yields more accurate records; tracings of the motion of the cardiac silhouette are well known as roentgenkymograms. The basic principle of roentgenkymography is as follows: A slit in a lead screen is placed in front of and perpendicular to the contour whose pulsation is to be recorded. A film moves in a direction perpendicular to that of the slit. The motion of that point of the contour on which the slit has been centered is recorded by the x-ray beam incident on the film passing across the slit.

Goett and Rosenthal[1] used a single slit, while Hitzenberger and Reich[2] and Zdansky and Ellinger[5] used two slits. Stumpf[4] constructed a screen containing several horizontal slits a distance of 12 mm. from each other so that kymographic records of the entire cardiovascular silhouette were obtained. Cignolini[6] invented another multiple-slit apparatus where several slits could be adjusted over points of greatest interest on the cardiac silhouette.

Roentgenkymography was received with great hope, but its limitations were soon recognized. These are of two kinds: those due to anatomic and physiologic conditions and those inherent in the technique applied. The anatomic and physiologic limitations are: (1) Linear movement can be registered graphically in its true excursion only if it is observed perpendicularly to the direction of its progression. If observed at any other than a right angle, the excursion will appear to be smaller than it really is. (2) Only the pulsation of the visible con-

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*Various names may be found in the literature for tracings obtained by means of the fluoroscope and the photoelectric cell.[8-13] The best known designation for the method is the name suggested by Henny and Boone,[10] "electrokymography." We have felt that the name should designate the main field of application (cardiology) without omitting the roentgenologic aspect of the method. We have, therefore, proposed[14] the term "fluorocardiography."

tours may be registered, so that no conclusion as to the total change in volume of a chamber may be drawn. (3) Pulsations and changes in volume of the cardiac chambers and large vessels are transmitted to adjacent structures; this is particularly true of the transmission of ventricular pulsations to the auricles. The pulsations observed at the surface of these structures often represent a summation of their own weak pulsation plus all transmitted pulsations. (4) The heart performs several types of movements, such as rotation, lateral shift, and elevation of its apex. Also, the effect of respiration on heart motion must be taken into account. These movements distort those solely due to changes in volume of the chambers. These considerations make it clear that the amplitude and even the direction of individual pulsations may be subject to complicated distortions and that any evaluation of the tracings must take into consideration all of these sources of interference.

The limitations in the use of roentgenkymography consequent to technical factors are (1) the difficulty of applying the apparatus in a position perpendicular to the contour to be plotted because of the rigidity of the slits; (2) the short duration of the records obtained (only three or four cycles in Stumpf's multiple-slit kymograph); (3) insufficient speed of the tracings; and (4) inability to simultaneously record on the same film other tracings of the cardiac action (electrocardiogram, heart sounds, pulse waves, and so forth). Attempts have been made[5,6] to overcome these weaknesses by faster recording over a longer period of time, or by densometric transcription of the original records,[4] but no great improvement resulted.

Various attempts have been made in the last fifteen years to record fluoroscopic phenomena by means of phototubes. The first of these, by Hjelmare[8] in 1932, was unsuccessful, while the second attempt, by Heckmann[9] in 1937 (actinography), was also soon abandoned.

In 1945, Henny and Boone[10] made a significant advance when they used a multiplier phototube with a slit connected with the electrocardiograph; a simultaneous carotid pulse tracing was used for the timing of the waves. The apparatus was called an electrokymograph. An improved version of this apparatus has been described recently by Henny, Boone, and Chamberlain,[11] who reported on clinical studies in progress.

Other roentgenkymographic devices which operated on the photoelectric principle were described in 1946. Lian and Minot,[12] used a phototube connected with a galvanometer for the study of cardiovascular phenomena; they called their method radioelectrokymography and used the electrocardiogram as a timer. Marchal[13] used a very sensitive apparatus for the study of pulmonary vascular phenomena; he called his method kinedensigraphy.

THE APPARATUS

The transducer employed in this investigation is fundamentally the Henny, Boone, and Chamberlain electrokymograph, plus modifications made in order to increase the sensitivity or magnitude of amplification. However, increased sensitivity proportionately increased the amount of artefact, and complete freedom

from artefact is imperative for accurate study of slight motions and variations in density, especially in the oblique positions. The modifications that were finally introduced primarily deal with increasing the ratio between artefact level and degree of amplification (Fig. 1).

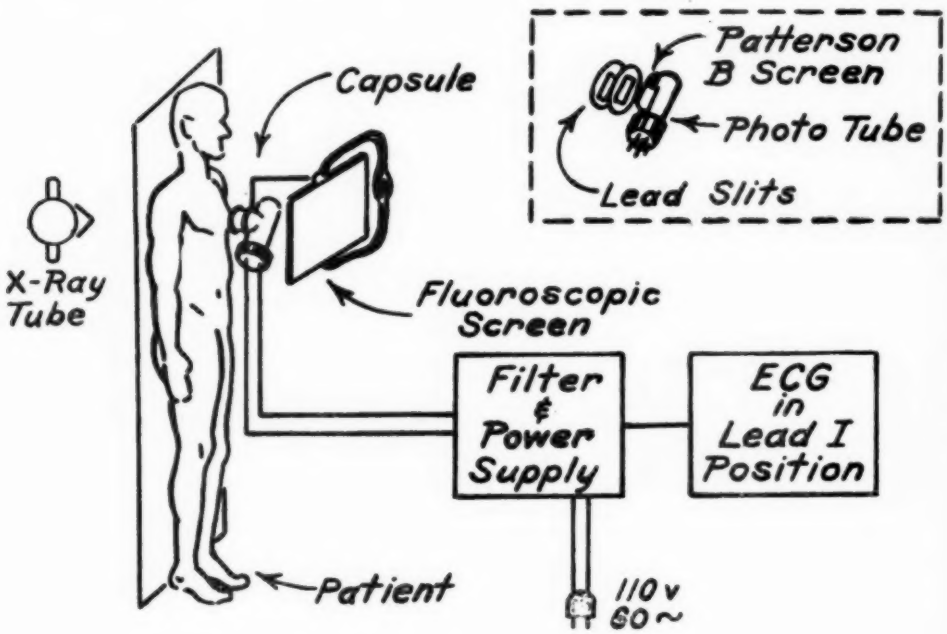

Fig. 1.—Schematic diagram of the arrangement for taking fluorocardiograms.

The transducer was coupled to either a Sanborn Stethocardiette or a Tri-Beam Stethocardiette. The Stethocardiette was used for simultaneous phonocardiogram and fluorocardiogram registration. The Tri-Beam apparatus was used when an additional pulse tracing or fluorocardiogram was desired.

The apparatus is so arranged that when the long axis of the slit is placed in the direction of motion of the portion of the silhouette being studied, a contractile motion registers as a downward or negative wave. If the slit is placed completely within the silhouette area, *densograms* are registered; an increase in density registers as an upward or positive wave and a decrease in density as a downward wave.

As in the Henny, Boone, and Chamberlain electrokymograph, the main part of the apparatus is an electron multiplier phototube.* This is a high vacuum bulb similar in physical appearance to the conventional radio tube. Internally, it consists of a light-sensitive photocathode, a system of nine secondary emission electrodes called dynodes, and a collector anode. The phototube has a maximal response to light, with a wave length of 4,200 Angstroms which is in the blue region.

*This tube is produced by the Radio Corporation of America, Camden, N. J., and is designated 931-A.

The sensitivity of the phototube is 8,200 microamperes per microwatt and the maximum luminous sensitivity is 10 amperes per lumen. The electron multiplier is capable of a maximum current amplification of approximately one million times. The sensitivity of the photocathode to green radiation (approximately 5,000 Angstroms) is about 70 per cent of the maximum response in the blue portion of the light spectrum.

When the photocathode is exposed to light, a proportionate number of electrons are released and immediately attracted to a dynode which is at a positive potential with respect to the photocathode. The surface of the dynode is treated for secondary emission so that each electron which originates at the photocathode displaces several additional electrons at the first dynode. These secondary electrons are then directed to a second dynode which is at a potential more positive than the first dynode surface and they, in turn, displace many more electrons. Since this multiplication process is cumulative in the nine stages of amplification, the maximum overall current amplification attainable is approximately one million times.

As was done by Henny, Boone, and Chamberlain with different types of screens, a strip of Patterson B screen is cemented to the glass envelope of the electron multiplier phototube directly in front of the photocathode. When the x-rays strike the fluorescent screen, the light emitted by the screen is picked up by the photocathode and transformed into equivalent photoelectrons and amplified by electron multiplication. Thus, the electrical output of the 931-A tube varies in proportion to the movement of the silhouette within the opening of the slit. The output of the tube is, in turn, fed into the electrocardiographic channel through a potentiometer which functions as a sensitivity control.

Densograms of the silhouette are registered in a similar manner. The strip of Patterson B screen gives off more or less light to the photocathode as the transparency of the silhouette varies.

As has been observed by Henny, Boone, and Chamberlain, the question of interference elimination is obviously of utmost importance. There are three forms of interference which must be eliminated, namely: (a) electrostatic radiation from the high tension x-ray equipment; (b) flicker due to the cyclic discontinuity of the x-ray emanations; and (c) fluctuations of the power line.

The elimination of interference caused by the high tension x-ray equipment was the least difficult in that only complete electrostatic shielding of the electrokymographic circuit was necessary. A well-shielded electrocardiograph apparatus will not pick up this electrostatic radiation, provided the input circuit is completely shielded. Similarly, the piezoelectric type sphygmographic attachment,[17,19] which may be used simultaneously on the three channel recorder, is a completely shielded component which is the input to an electrocardiographic channel. The phonocardiographic channel, which is systematically used by us, is likewise shielded and completely free of electrostatic interference. Modern roentgenoscopes are sufficiently noise-free as to produce negligible artefact in the phonocardiograms.

The anode potential supplied to the x-ray tube may be obtained by full-wave or half-wave rectification. A full-wave rectifier applies to the anode of the

x-ray tube pulses which are twice as frequent as those of the power line. That is, if the frequency of the power line is 60 cycles per second, the output of the full-wave rectifier is 120 pulses per second. A half-wave rectifier, on the other hand, supplies 60 pulses per second to the anode of the x-ray tube if the power line is of the 60 cycle per second variety. Thus, the fluorescent screen flickers either 120 or 60 times per second, depending upon whether full- or half-wave rectification is used.

For ordinary roentgenoscopic application, the flicker is of no consequence because the human eye cannot perceive it. However, in this transducer the flicker is transformed into a cyclic interference in the tracing. The magnitude of flicker is so much greater than that of the waves of the tracing that the latter are completely masked.

Henny, Boone, and Chamberlain, in order to suppress the flicker interference, employed a tuned filter. The characteristics of the filter they used permitted a maximum attenuation of the flicker interference approximately one thousand times. When the transducer with increased amplification was used, we found that one thousandfold attenuation was inadequate with the degree of amplification we used. As a result, to make possible the registration of slight silhouette movements or density variations imperceptible to the eye, a two-stage resistance-capacitance type parallel-T network attenuator was found necessary. The essential differences between the filter used by Henny, Boone, and Chamberlain and the one used in our models are: (a) Our filter attenuates the 60 or 120 cycle per second interference at least *one hundred thousand times*, as compared with an attenuation of *one thousand times* in the Henny, Boone, and Chamberlain model. (b) The configuration and spectral width of the filter used in our tests affects the overall response speed to a lesser degree than does the Henny, Boone, and Chamberlain model for equal magnitudes of attenuation.

The significance of (a) is obvious and needs no further discussion. The technical analysis of item (b) is rather complex; however, the significance may be illustrated as follows: If the galvanometer which is used in conjunction with the transducer has a deflection speed of 0.01 second, we observed that the effective speed due to the tailing off of the filter envelope when the filter was tuned to 120 cycles per second was approximately 0.02 second. If the filter is tuned to 60 cycles per second, the effective galvanometric speed is reduced by a greater amount. Our tests showed that the "tailing off" effect present in the Henny, Boone, and Chamberlain filter modified the speed more than did ours. This phenomenon is an extremely important consideration, especially when fluoroscopes with half-wave rectification are used. It should be stated here that a thorough investigation must be made to determine what the minimum effective speed must be so that the tracing will not be distorted. Of course, the introduction of equalizer circuits may minimize or completely eliminate any possible distortion. Also, filter systems which are more free of the "tailing off" effect may become available.

If electrocardiograms are to be taken simultaneously with the fluorocardiograms, similar attenuators must be interposed between the subject and the electrocardiographic apparatus. Otherwise, the unshielded patient will pick up

sufficient electrostatic radiations from the high tension components of the x-ray equipment to completely mar the electrocardiogram.

The graduated potentials that are applied to the nine dynodes of the electron multiplier phototube are obtained from the alternating current power line. That is, the power line potential is transformed to the appropriate voltage, then rectified, filtered, and divided among the electron multiplier elements. Due to the extremely low frequency amplification that the apparatus must employ in order to register the minute changes in the silhouette, the potentials that are applied to the phototube elements must be well regulated. Commercial power lines are known to have instantaneous voltage fluctuations to the extent of several volts. These fluctuations must be regulated or smoothed out before application to the phototube elements or they will register graphically in superposition upon the waves of the tracing. Since these fluctuations are several thousand times as large as the potential variations emitted by the photocathode when registering slight silhouette changes, they would completely mar the record.

Henny, Boone, and Chamberlain regulate the line voltage fluctuations by means of a voltage regulating transformer which is interposed between the electrokymograph and the commercial power line. These stabilizing transformers are in common use in electrical equipment and are commercially available from transformer manufacturers. The common variety of regulating transformer is rated to maintain the output voltage within plus or minus 1 per cent for a total primary variation of 30 per cent. Specially adjusted regulating transformers may be obtained in which the regulation is improved to approximately 0.5 per cent. We observed that the degree of regulation obtainable with a regulating transformer was insufficient to eliminate all the effects of line voltage fluctuation when the sensitivity of the transducer was increased. The line voltage fluctuations were regulated in our experimental models to a point at which the maximum fluctuations, whether instantaneous or gradual, produced insignificant artefact in the tracing. This was accomplished by electronic regulation, which is capable of regulating voltage variations much more effectively than is possible with the transformer method. There are several well-known methods for obtaining electronic regulation which are well described in the electronic literature.

Van Allen[16] in his investigation on different types of fluoroscopic screens for their phosphorescence or lag, found that the green fluorescent Patterson type B screen showed the smallest amount of lag. The result of Van Allen's studies demonstrates that the error due to phosphorescent lag is less than 1 per cent in our device.

Increased sensitivity was obtained in our experimental models by optimum impedance matching between the electron multiplier phototube and the registration apparatus. The loading of the electron multiplier in the Henny, Boone, and Chamberlain electrokymograph creates a severe mismatch with resultant loss in amplification, especially when the string galvanometer is employed without a stage of electronic coupling.

Henny, Boone, and Chamberlain have employed the pulsations of the right carotid artery for timing the waves of their electrokymograms, which were registered by means of a mechanical-optical device. Even though the piezoelectric sphygmogram, as described by Miller and White,[17] is free from the errors inherent in the mechanical-optical system, we chose the phonocardiogram for timing the waves of our tracings. The transmission time of the cardiac sounds in the chest is so infinitesimally small as to be unmeasurable with the registration techniques employed for this type of work. Also, Rappaport and Sprague[18] have shown that the first and second heart sounds may be broken down into events which are of considerable aid in timing the phases of cardiac action. Of course, the third heart sound and auricular sound that often are present in the phonocardiogram may also aid in timing these phases. The phonocardiogram, therefore, is capable of timing practically every mechanical event in the cardiac cycle, which is not true of the sphygmogram.

TECHNIQUE OF APPLICATION

The pickup device (Fig. 2) is attached to a standard fluoroscopic screen by means of a brace. It is centered on the screen so that it is fully exposed to the x-ray beam with the fluoroscopic diaphragm narrowed down to a small field. The slit may be placed either across the border of a moving shadow or fully against the center of the latter. In the latter instance, the tracing is a *densogram*.

Healthy individuals and patients were studied both in the recumbent and sitting positions, the procedure being essentially the same in both instances. A revolving stool was used for studies made with the patient in the sitting position. For every positioning of the pickup device, the shutter is opened for orientation and narrowed again as soon as the slit is brought into position.

As a routine, with the patient in posteroanterior position, we start on the left side, first plotting the apex of the heart just above the diaphragm (Fig. 3); another tracing on the upper part of the left ventricle is then taken. This study is followed by that of the appendage of the left auricle, which often is better visualized by a 10° to 15° rotation toward the left oblique position. The pulmonary artery usually is visible, but sometimes it is advantageous to turn the patient toward the right oblique position through an angle of 10 to 15 degrees. Next, the aortic knob, corresponding to the distal portion of the aortic arch, is easily brought into position. The descending aorta can be studied in the left oblique position by placing the slit vertically either against the spine or between it and the heart. We then have a *densogram* of the aorta (Fig. 4).

On the right side we usually trace the right auricle at its most prominent point; occasionally, also at a lower point of its contour. In some cases a good tracing is obtained by using the uppermost portion of the right auricle with some rotation toward the left oblique position; in this case we assume that we are centering upon the appendage of the right auricle.

The ascending aorta can be studied in normal young subjects by using a 10° left oblique position. Its study in the posteroanterior position is possible in mature or old individuals when atherosclerosis and dilatation of the vessels are present.

Fig. 2.—The fluorocardiograph. The pantograph and capsule arrangement, which is normally fastened to the screen of the fluoroscope, is here shown above the control panel of the apparatus.

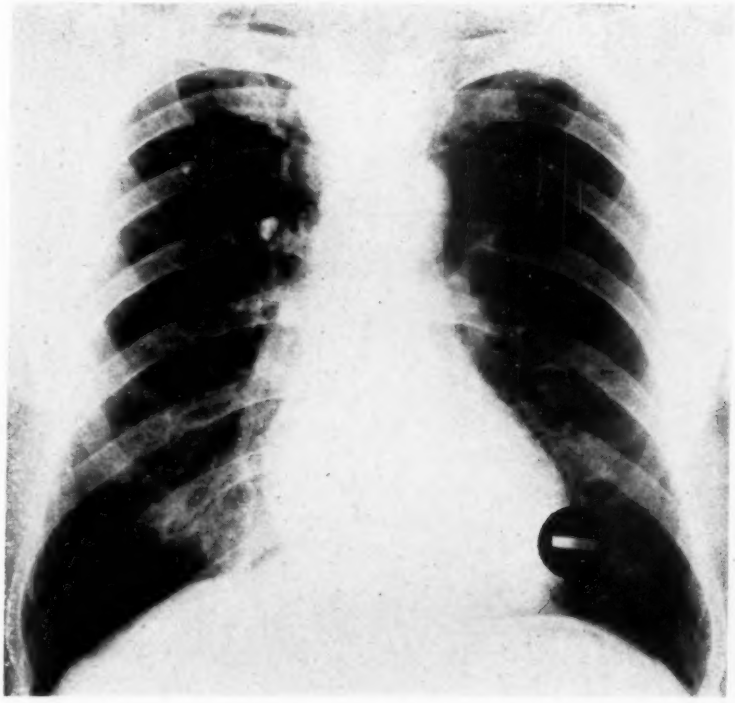

Fig. 3.—Chest film in posteroanterior position. The slit of the schematic pickup device is placed at the cardiac apex.

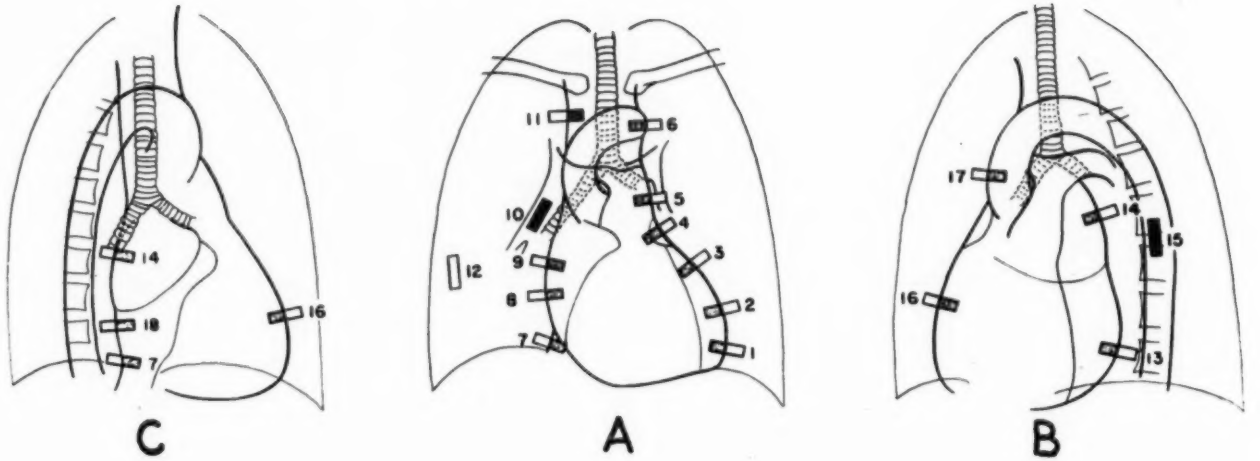

Fig. 4.—Standard positions of the slit for recording the motion of various cardiovascular and pulmonary structures. *A*, Postero-anterior position: (1) apex; (2) left ventricle, half way position; (3) left ventricle, upper portion; (4) left auricular appendage; (5) pulmonary arch; (6) aortic arch; (7) inferior vena cava; (8) right auricle, mid-portion; (9) right auricle, upper portion; (10) right hilar shadow (densogram); (11) superior vena cava; and (12) right lung, lower lobe (densogram).

B, Left anterior oblique position: (13) left ventricle, posterior wall; (14) left auricle, posterior wall; (15) descending aorta (densogram); (16) right ventricle, anterior wall (this is usually plotted in the straight lateral view at the level indicated by the diagram); and (17) ascending aorta.

C, Right anterior oblique position: (7) inferior vena cava; (14) left auricle, posterior wall; (16) right ventricle (see note in left anterior oblique); and (17) right auricle, posterior wall.

We have not always been successful in obtaining a satisfactory tracing of the superior vena cava. In addition to greater deflections, similar to those of the jugular phlebogram, there are often a large number of additional vibrations. Since we were working with healthy young individuals, it was occasionally difficult to visualize fluoroscopically the vena cava clearly enough to place the pickup unit correctly. On the other hand, we found it easy to obtain excellent tracings of the inferior vena cava which is seen either in the straight postero-anterior or in the right oblique position. The patient holds his breath in deep inspiration for this procedure.

For the plotting of the hilar pulsations, we preferred the right hilar shadow as the one more clearly exposed. With the intention of plotting a densogram of the hilar vascular convolution as a whole, the slit was placed vertically across the hilar vessels as far away from the vascular shadow as possible.

For the recording of the peripheral pulmonary pulsations, the slit was placed vertically, either over the upper or the lower lobe of a lung, a few centimeters above the diaphragm. This tracing is a *densogram* of the lung.

For better exposure of the left auricle we chose a right oblique, sometimes almost a lateral, position, and placed the slit from 3 to 4 cm. below the level of the bifurcation of the trachea across the contour of the auricle where it is well seen against the clear space of the right bronchus. Whenever the left auricle is extremely dilated and its borderline is not clear, a *densogram* of the chamber is recorded. In many cases, however, the left oblique position is sufficient for a good tracing.

The pulsation of the right ventricle is best picked up in the straight lateral view just above the point where it separates from the anterior chest wall. For reasons not entirely explained so far, we have not been always successful in obtaining a satisfactory tracing of the right ventricle with a normal subject in a sitting position, although there has been no difficulty in obtaining a satisfactory one with the subject in the recumbent position. However, patients with right ventricular hypertrophy usually yield good tracings in the sitting position. Actually, the tracing of the right ventricle is often a *densogram* of this chamber.

The roentgen exposure of the skin of the patient during this procedure is within safe limits. Our ordinary routine technique for chest fluoroscopy is used, that is, 5 milliampere at 65 to 70 kilovolts with an inherent filter of 1 mm. of aluminum. The orienting fluoroscopy with the wide open shutter takes only a few seconds. With the pickup device in place, the shutter is narrowed to an opening of about 25 square centimeters. The actual recording does not require more than two minutes, including the adjustment of the amplifier. Thus, with the portion of the skin changing with each position of the pickup device, the dose applied to the skin is within safe limits.

INTERPRETATION OF THE TRACINGS

The polarity of the apparatus is arranged so that an increase in light causes a downward movement of the tracing. Therefore, any fall in the curve indicates either an inward motion of the cardiac border if the slit is across the border

of the cardiac silhouette, or a decrease in the thickness of the structure if the slit is over a homogenous area, and a densogram is recorded. On the other hand, every rise of the curve indicates either expansion of the cardiac or arterial border or increased thickness of the structure (densogram).

Any kymographic wave occurring before the first large vibration of the first sound, as recorded in the phonocardiogram, is presystolic; any wave occurring after the last vibration of the second sound is diastolic; any wave taking place between the beginning of the first sound and the end of the second is systolic.

The tracing has no well-defined baseline. An arbitrary zero line can be made by drawing a line, passing through that point of the curve which is between the auricular and the ventricular waves of the cardiac tracing (if the rhythm is normal). Its equivalent point, namely, the point from which the venticular wave begins, can be used if there is no auricular contraction. The foot of the wave will mark the zero point in the tracings taken over the arterial tree of the lung.

We feel that the method is simple, accurate, and satisfactory in the study of cardiac and vascular pulsations.

SUMMARY

Utilizing the Henny-Boone method, but with some modifications, an apparatus has been built which is capable of recording minute pulsations imperceptible to the naked eye. The tracings are obtained by the use of the fluoroscope, an electron multiplier photoelectric cell, a screen with a slit, and a phonocardiograph-electrocardiograph. A technical description of the apparatus and a list of the modifications are given.

As a routine procedure, the phonocardiogram was found preferable as a timer because it is accurate, easy to record, and in close time relation with the valvular events of the heart. The tracings are recorded at a film speed of 75 mm. per second.

The name *fluorocardiography* is suggested for the method, as being more descriptive than previously employed terms.

The pulsations of the following structures have been studied: (a) left and right ventricles; (b) left and right auricles; (c) pulmonary artery; (d) aorta (ascending, arch, and descending); (e) superior and inferior venae cavae; (f) hilar shadows; and (g) pulmonary parenchyma.

The optimum positioning of the slit for obtaining clinically relevant records is discussed. These may be obtained either by placing the slit across the visible border of the visible silhouette or entirely within the shadow of a structure; the latter are *densograms*.

We wish to thank the Sanborn Company of Cambridge, Mass., for their generous help and friendly cooperation. We also wish to thank Doctors W. E. Chamberlain, B. R. Boone and G. C. Henny of the Temple University Medical School for generously putting at our disposal initial unpublished information of a technical character.

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FLUOROCARDIOGRAPHY (ELECTROKYMOGRAPHY)

II. Observations on Normal Subjects

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IN PREVIOUS communications[1,2] the authors, following the initial work of Henny, Boone, and Chamberlain,[6,7] have discussed certain of the technical aspects of photoelectric roentgenkymographic tracings which Henny and associates have termed "electrokymograms" but for which we have proposed the term "fluorocardiograms" as being more descriptive. In these reports, the basic Henny, Boone, and Chamberlain electrokymograph and our modifications have been described. In addition, the x-ray technique and the preferable positions for registering the pulsations of the various portions of the cardiac border, the large vessels, and the lungs are discussed. As a routine procedure, we have used the phonocardiogram as a means for timing the component waves. The physiologic observations which follow are based upon a study of twenty normal subjects whose ages ranged from 15 to 70 years.

GENERAL CONSIDERATIONS

As we have already pointed out,[1,2] roentgenkymographic tracings of any point of the cardiac silhouette may represent the summation of: (a) Motion due to changes in volume of the chamber in systole and diastole; (b) motion due to rotation and total shift of the heart; and (c) traction resulting from motion of other adjacent cardiovascular structures. The possible causes of traction of any structure upon another are many; in particular, one auricle may show the effect of traction by a ventricle or by the large arteries. These distortions of the pulsatory phenomena proper have been established by classical roentgenkymography (Fig. 1).

The visible changes in volume are greatest in the left ventricle, and decrease in the following order: (a) left ventricle, with highest amplitude at the apex; (b) aorta; (c) pulmonary artery; (d) right ventricle; (e) auricles; (f) venae cavae and hilar shadows; and (g) lungs (Figs. 2 and 9).

These movements may be seen by fluoroscopy for the most part, but detailed analysis is possible only by graphic tracings which are accurate as to time and amplitude.

Read at the Twentieth Annual Scientific Meeting of the American Heart Association, Atlantic City, N. J., June 6 and 7, 1947.

From the Department of Radiology and the Medical Service, Beth Israel Hospital, Boston, Mass.

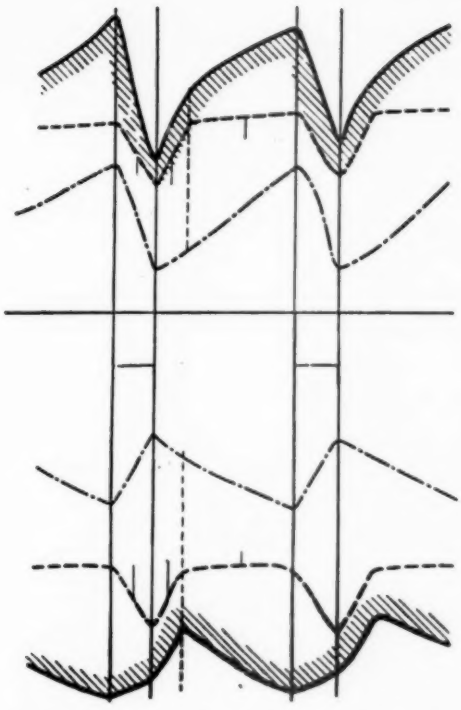

Fig. 1.—Heckmann's scheme of the motion of the left (above) and right (below) heart borders in the roentgenkymogram. The shaded line represents the actual tracing which is the resultant of volumetric changes (dot-dash line) and of positional changes (broken line). (from Roesler, Hugo: Cardiovascular Roen'genology, Springfield, 1945, Charles C. Thomas, Publisher.)

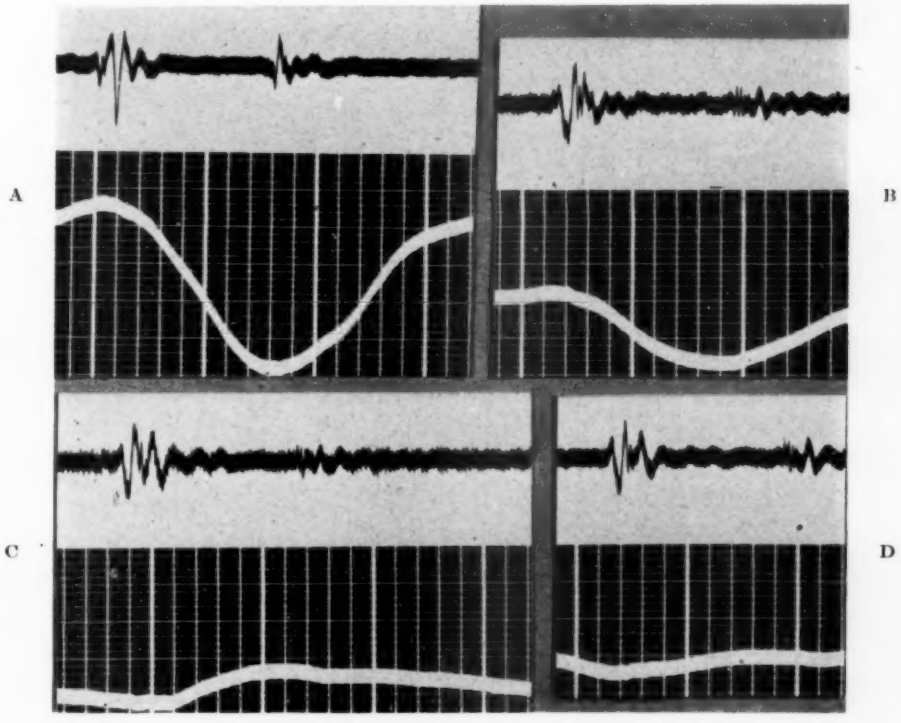

Fig. 2.—Comparison of four tracings recorded on the same individual with the same amplification. *A*, Apex; *B*, high left ventricle; *C*, aortic arch; and *D*, pulmonic arch.

The phonocardiogram in *A* appears somewhat different in configuration, although taken on the same subject. This is due to relocation of the microphone for optimum visualization of the heart. Similar phonocardiographic differences will occur in the subsequent illustrations for this reason.

SPECIAL ANALYSIS

Left Ventricle (Fig. 3).—

Apex: Slight differences can be found between the fluorocardiograms registered in the supine, and those taken in the sitting position. In general, a small positive wave can be recorded either immediately before or during the first group of vibrations of the first sound-complex. The most logical interpre-

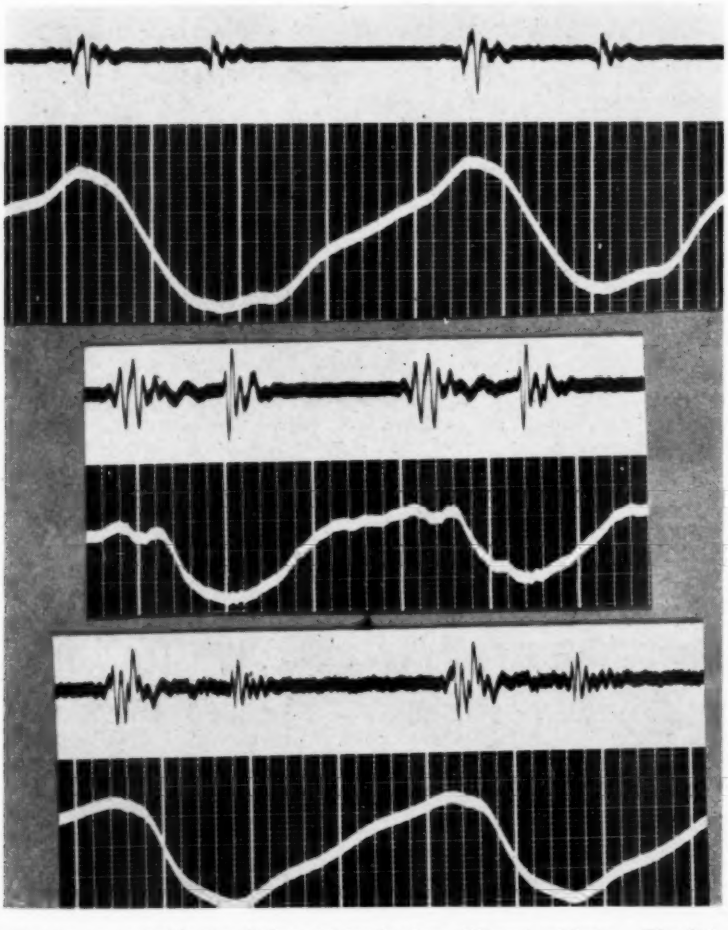

Fig. 3.—Tracings recorded in the sitting position in three different subjects. The distention of the ventricular wall because of auricular contraction is mainly apparent in tracing *B*. Tracings *A* and *B* were recorded at the apex. Tracing *C* was taken in Position 3.*

tation is that the left auricular contraction pushes a certain amount of blood into the left ventricle, causing a dilatation of its apical region; tracings recorded on patients with auricular fibrillation do not show this small positive wave. The tension period (isometric contraction) of ventricular systole is evidenced by the small depression, probably because of slight torsion of the heart (Fig. 3, *B*).

*This and other positions which will be referred to have been described in a previous paper.[2]

In a tracing recorded at the apex, the main ventricular wave consists of a large downward deflection which starts at the end of the first sound-complex if this is short, or at the time of the second largest vibration of the same sound; this has been explained as due to the opening of the aortic valve.[4] There is, therefore, a striking coincidence between the phases of the fluorocardiogram and those of the phonocardiogram. The beginning of the ventricular wave is due to the decrease in volume of the ventricular mass.

The descending branch of the ventricular wave reaches its lowest point at a time which varies in different subjects and positions. It is apparent that rotation and displacement of the apex, in addition to volume changes, influence the true relationship of the point of maximal fall. In most cases, this point coincides with the largest vibration of the second sound-complex, that is, with the closure of the aortic valve. This precise coincidence, which is more commonly seen with the subject in the sitting rather than in the lying position, proves that the tracing of the volume changes of the left ventricle is accurate in its timing. In some subjects, particularly when they are examined in the supine position, the maximal drop takes place after the completion of two-thirds of ventricular systole and is followed by either a shallow curve or a gently ascending slope. Frequently in the latter cases, a small notch is present at the time of the second sound.

The return of the tracing to the base line does not occur evenly: first, there is a rapid slope which ends at the time of the third heart sound if this sound is present (rapid filling of the left ventricle); this is followed by a more gradual slope, or even a horizontal line, which continues until the beginning of the following cycle. In some cases, a little rebound is present at the beginning of diastole.

Densogram: The densogram of the left portion of the ventricular mass resembles an apical tracing. However, the ascending limb of the curve (diastole) is slower and reproduces less accurately the events of the cardiac cycle.

Convexity of the Left Ventricle: When the slit is placed higher on the convexity of the left ventricular silhouette, the undulations of the tracing reproduce the volume changes of the chamber more faithfully and denote to a lesser degree the extraneous effect of the motion. The total depth of the ventricular wave is approximately 40 to 50 per cent of that recorded at the apex (Fig. 3, *A* and *C*). The coincidence between the lowest point of the ventricular wave and the main vibrations of the second sound is seen more regularly in this position.

Other Points on the Ventricular Surface: The left ventricle can be studied in various projections, such as the left anterior oblique (posterior aspect) and the right anterior oblique at 20° or the left posterior oblique (anterolateral aspect). Tracings recorded in these positions give basically the same type of tracing as that of the left margin in the posteroanterior position, except that the waves are smaller and the lowest point of ventricular systole frequently is represented by a shallow curve rather than a sharp angle.

Right Ventricle (Fig. 4).—The study of right ventricular contraction is far more difficult than that of the left. Indirect evidence of right ventricular activity may often be found in the tracings of the right auricle in the postero-anterior view; however, they cannot be considered accurate, even in cases of auricular fibrillation. The best tracings are recorded in the straight lateral view with the slit placed where the cardiac shadow separates from that of the anterior chest wall, or just below this spot. Recording of a slightly higher segment in normal individuals frequently has yielded tracings of an arterial type (pulmonary artery). We feel that the tracings of the right ventricle are a composite of the pulsations of the contour plus a densogram of the anterior part of the right ventricle.

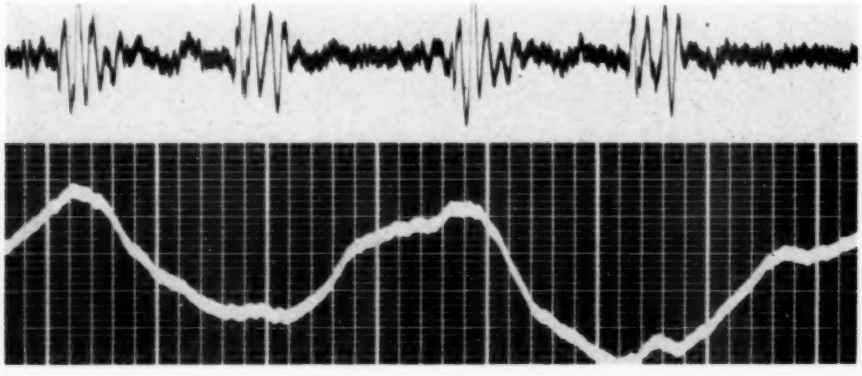

Fig. 4.—Tracing of the right ventricle in Position 16.

The tracing of the right ventricle presents only a small positive wave at the beginning of the first sound-complex. Later, it shows a curve comparable to that of the left ventricle in all details. The absolute amplitude of the right ventricular wave is far less than that of the left. This is not evident in our tracings because higher amplification is displayed except in instances of comparative studies.

Left Auricle (Fig. 5).—Studies of the left auricle were made in three different positions: (a) in a *10° left oblique* (left auricular appendage); (b) in *left oblique*, at 45 or more degrees; and (c) in *right oblique*, at 45 or more degrees.

While the tracings of the three positions are similar, one of the three is sometimes inferior to the others because of individual conditions.

The typical tracing shows a downward wave which occurs in the presystolic portion of ventricular diastole. This auricular wave is rounded and small in some subjects, but is deep and sharp in others. The beginning of the auricular wave is about 0.14 second before the first sound. However, if the heart rate is rapid, there is no sharp distinction between early diastolic and presystolic waves: only one slow wave is present in diastole with maximum depth at the time of maximum left auricular contraction. The peak of the downward auricular wave is reached either at the time of the first vibration of the first sound-complex or

slightly before. If an auricular sound is present, it is seen during the downward slope of the auricular wave. The presystolic wave is much deeper in patients with left auricular hypertrophy, while it disappears in patients with auricular fibrillation.

After the presystolic wave, the tracing rises, sharply at first, then slowly up to the middle of ventricular systole; it often presents two negative waves, one in systole and the other in diastole.

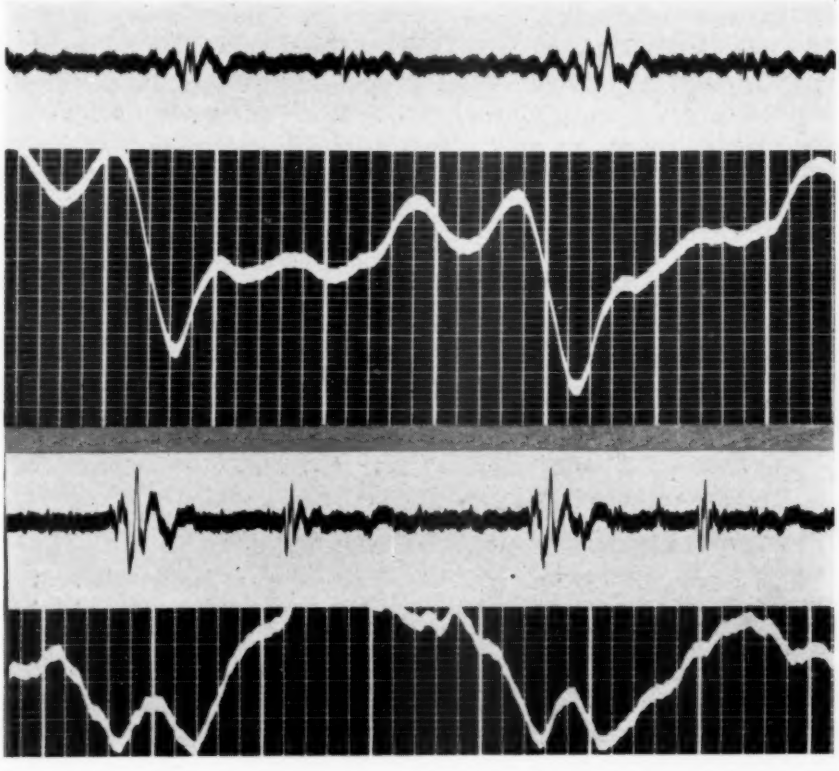

Fig. 5.—Tracings of the left auricle: *A*, Tracing recorded in Position 14 with the subject sitting; *B*, Tracing recorded in Position 4 with the subject lying. Tracing *A* presents a very deep presystolic wave and nearly no trace of ventricular activity. Tracing *B* shows two negative waves, one presystolic, and one in early systole; after the latter, the tracing rises gradually until after the second sound. In both tracings, the auricular wave begins 0.10 second before the first vibration of the first sound-complex while the peak is reached about 0.02 second before it.

The systolic wave of the left auricular tracing is related to the dynamics of the left ventricle. The contraction of the left ventricle lowers the auriculo-ventricular septum; this creates suction within the left auricular cavity which is not immediately compensated for by increased inflow of blood. Therefore, an inward movement of the free auricular wall takes place. This is shorter in duration than the corresponding ventricular contraction owing to the venous inflow which dilates the auricle. The highest level of the tracing is reached not

at the end of ventricular systole, but slightly afterward when the mitral valve opens.

After the end of the systolic wave, a third negative wave may occur, the diastolic collapse. This probably is due to the passive flow of blood into the left ventricle when the mitral valve opens.

When the left auricle is greatly enlarged, but is not visible on the right heart border, and when its dorsal contour is not clearly visible, a densogram can be taken. Such a tracing presents a clear-cut presystolic downward wave. However, this is not as informative as a tracing of the contour, because of interference by the pulsations of the pulmonary veins and branches of the pulmonary artery.

The tracing of the left auricular appendage is sometimes not accurate during ventricular systole if the pulmonary artery is dilated; the record taken in the left oblique position may not be accurate during ventricular systole if the descending aorta is enlarged.

Right Auricle (Fig. 6).—The tracing recorded over the margin of the right auricle is similar to that of the left auricle. Contraction of the auricle during presystole is manifested by a small and rounded downward wave. After

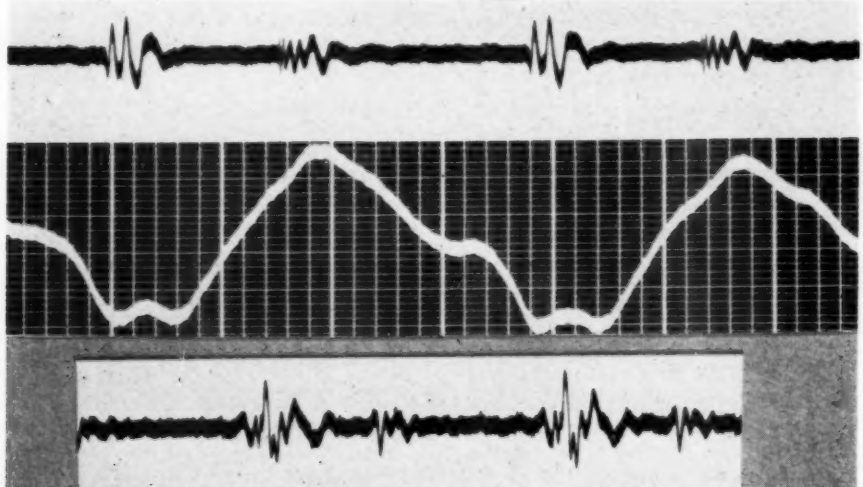

Fig. 6.—Tracings of the right auricle. *A*, 22-year-old man, in lying position. *B*, 15-year-old boy, in sitting position. In both cases the slit was placed in Position 8. The auricular wave is small in both cases, but is better visible in *A*. The ventricular wave is deeper in the sitting position. The maximum rise is reached after the second sound in both cases.

this, the tracing either reaches the base line or rises above it, but drops again during ventricular systole.

Ventricular systole is manifested by a sharp downward wave which often is deeper than the auricular wave. However, it terminates early at about mid-systole. The subsequent course of the auricular tracing varies with the position of the subject. In the sitting position, the tracing rises slowly and attains its maximum height at the time of tricuspid opening; in the recumbent position, the rise is quicker and there may be a convex line which brings the tracing far above the base line. Another drop, however, takes place after the opening of the tricuspid valve, the diastolic collapse.

In summary, there is a presystolic collapse, a systolic collapse, and, frequently, an early diastolic collapse. The early diastolic and the presystolic collapses are apparently due to changes in volume of the auricle, the former because of passive inflow from the right auricle into the right ventricle, and the latter because of right auricular contraction. The cause of the systolic collapse may be open to discussion. We feel that it is due mainly to a decrease in pressure within the auricle because of traction on the auriculoventricular septum, and not to a total displacement. Such a mechanism would give rise to an early end of the systolic wave, because the inflowing blood increases the auricular volume. The same mechanism explains the difference observed in the sitting and supine positions, because there is a greater and faster inflow from the inferior vena cava in the recumbent position.

Whenever there is tachycardia, the early diastolic wave merges with the presystolic wave, indicating that ventricular filling is continuous, first in a passive manner and later as a result of auricular contraction.

While evidence of right auricular contraction is often difficult to obtain by common clinical methods, we have always found a deep, sharp auricular presystolic wave in cardiac patients with sinus rhythm. On the other hand, whenever auricular fibrillation was present, no presystolic wave has been obtained.

Attempts to record a densogram of the right auricle are not always successful due to the superimposition of the right auricular shadow over that of the right ventricle.

Ascending Aorta (Fig. 7, *A*).—It is not always possible to record a tracing of the ascending aorta in the straight posteroanterior position in normal young individuals because of the fusion of the shadows of different structures. In the left oblique position, a tracing of the ascending aorta is usually possible.

When, however, the ascending aorta is dilated as a consequence of atherosclerosis, hypertension, or vascular syphilis, a tracing can be recorded both in the left oblique position and in the posteroanterior position. In such cases, the tracing is typical and the rise coincides exactly with the second large vibration of the first sound-complex or, if this vibration is not distinct, with the second half of this sound. The tracing of the ascending aorta may assume a plateau-like aspect.

Aortic Arch (Fig. 8).—The tracing of the aortic arch can be obtained in all subjects. It presents marked individual variation in its shape. Its common

features are: (a) a small positive wave during the first part of the first sound-complex, probably due to rising of the aortic valves at the time of isometric contraction; (b) a sharp rise, starting with the second large vibration of the first sound-complex (opening of the semilunar valves) and continuing until the end of the sound; (c) an anacrotic depression in the first part of systole; (d) a peak which usually occurs in the last part of systole but well before the second sound;

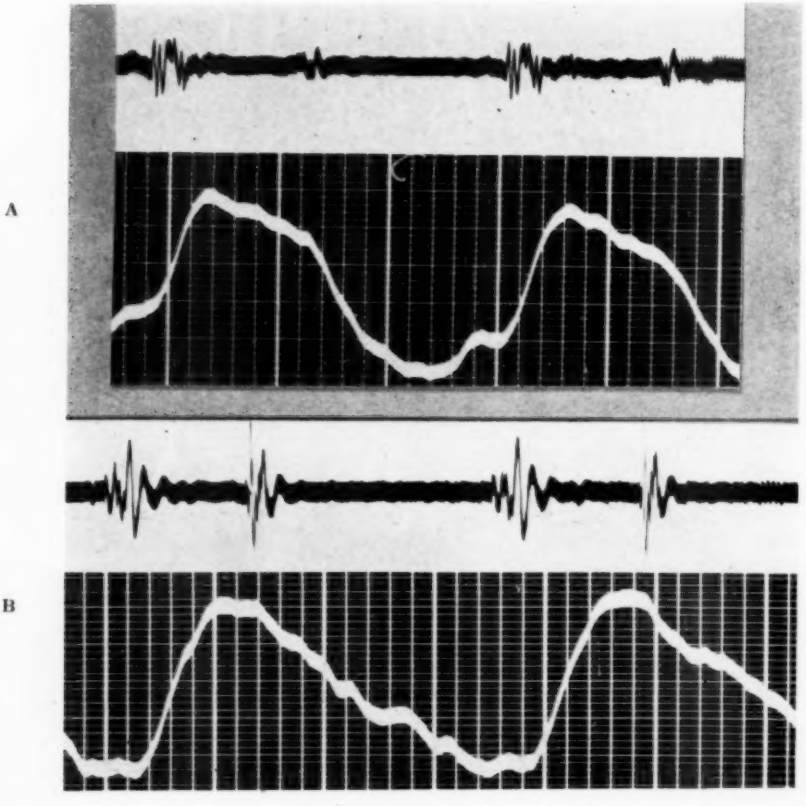

Fig. 7.—Tracings: *A*, of the ascending aorta in Position 17 (70-year-old woman) and *B*, of the descending aorta in Position 15 (25-year-old man). The rise of the pulse takes place at the time of the opening of the semilunar valves in Case *A* and 0.04 to 0.05 second later in Case *B*. The peak of the wave is reached 0.08 second after the opening of the semilunar valves in Case *A* and 0.18 second in tracing *B*.

(e) a predicrotic notch, which may coincide with the second sound or form a short pleateau, prolonged slightly after the second sound; (f) a dicrotic wave, which usually is small and rounded; and (g) a few small after-vibrations.

A comparative study of the fluorocardiograms of the aortic and pulmonary arches by simultaneous tracings, as well as by recording each of them simultaneously with the subclavian pulse, has shown a precession of 0.02 to 0.03 second in the rise of the pulmonic pulse over that of the pulse of the aortic arch.

A densogram of the aortic arch gives a tracing which is similar to that just described.

Descending Aorta (Fig. 7, *B*).—Since the descending aorta often does not present a sharp contour on fluoroscopy, only a densogram is possible in many normal subjects. The tracing is similar to that of the aortic arch, but shows a slight delay in the rise of the pulse in comparison with the rise in the arch.

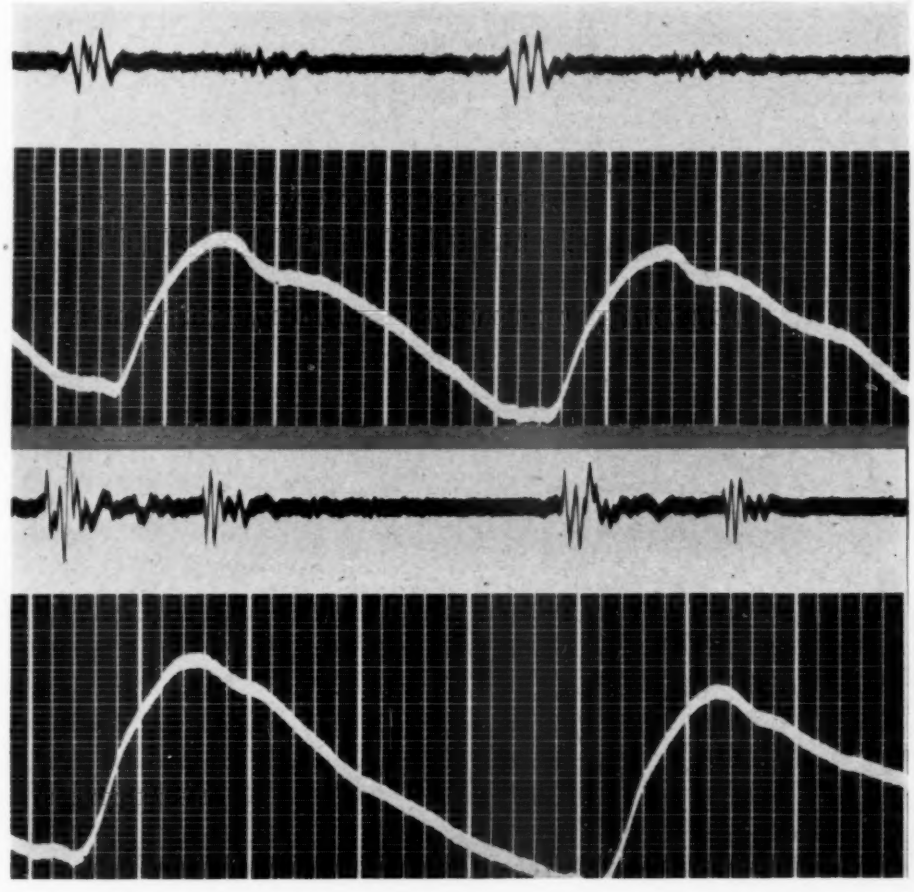

Fig. 8.—Tracings of the aortic arch (Position 6) in two different subjects. The rise of the pulse takes place 0.03 second after the opening of the semilunar valves in both cases. The peak is reached 0.02 to 0.03 second before the closure of the semilunar valves.

Pulmonary Artery (Figs. 9, *A* and 10, *A*).—The tracing of the pulmonary arch is usually easily obtained. Occasionally, a large left hilar shadow or a dilated descending aorta may distort the tracing. The pulsations of the latter structures, recorded as densograms in this instance, are of a much smaller amplitude and their influence on the tracing of the pulmonary artery consists only in a smoothing of the waves without other distortion.

The tracing of the pulmonary arch usually fails to show any upward wave during the first part of the first sound-complex. The pulmonic pulsation starts with the opening of the pulmonic valves (second part of the first sound-complex), then rises sharply, and occasionally shows a slight change of the slope which

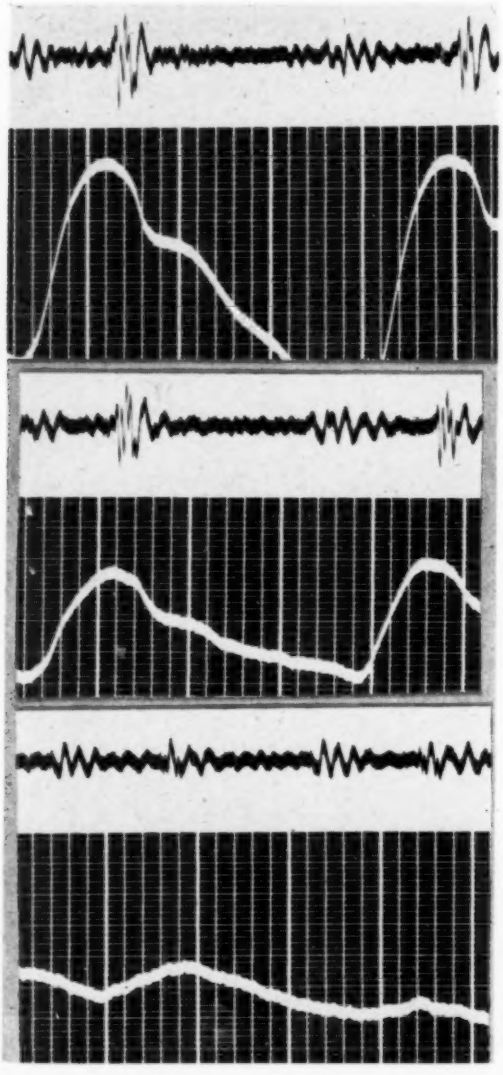

Fig. 9.—Tracings of the pulmonary artery, *A*, of the right hilar shadow; *B*, and of the right lung; *C*, recorded with the same degree of amplification.

is the equivalent of an anacrotic depression. The peak is reached after two-thirds of ventricular systole is completed. The predicrotic notch is usually deep and occurs 0.06 and 0.08 second after the main vibration of the second sound. The dicrotic wave is usually well defined and is higher than that of the aorta.

Its peak is usually from 0.10 to 0.12 second after the main vibration of the second sound. Another positive wave may be seen in late diastole before auricular contraction.

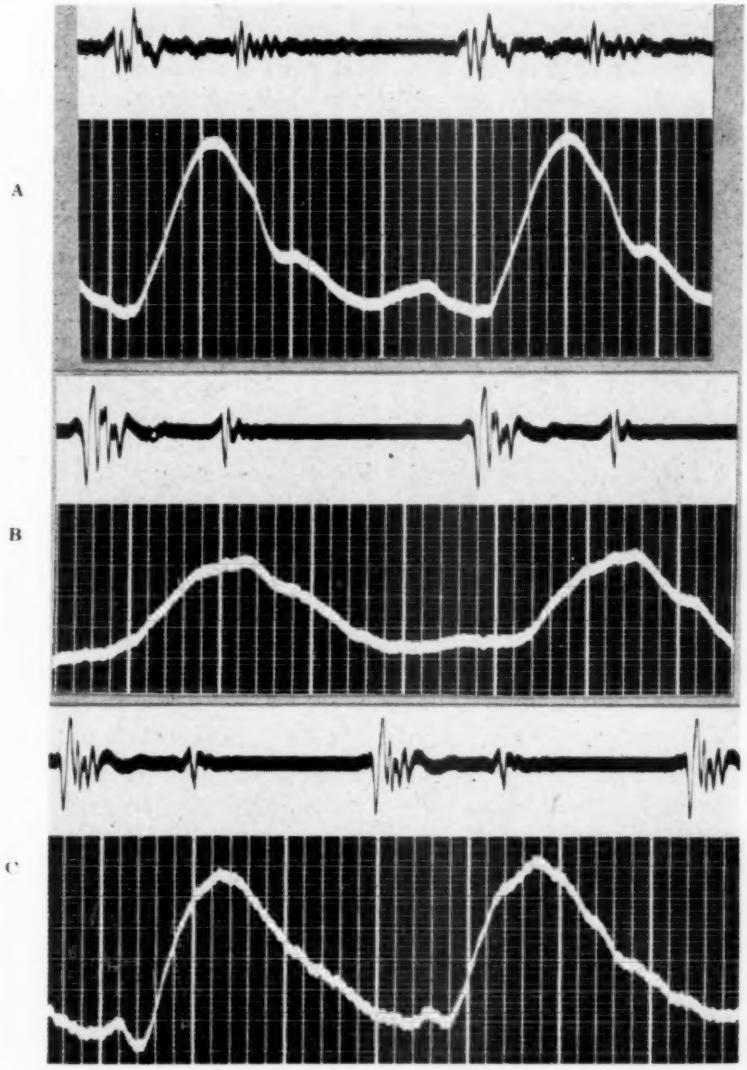

Fig. 10.—Tracings: *A*, of the pulmonary arch (Position 5); *B*, of the right hilar shadow (Position 10); *C*, of the right lung (Position 12). The rise of the pulse takes place 0.02 second after the opening of the semilunar valves in tracing *A*, 0.07 second after it in tracing *B*, and 0.11 after it in tracing *C*. The peak of the pulse occurs 0.06 second before the closure of the semilunar valves in tracing *A*, 0.06 second after this event in tracing *B*, and 0.08 second after it in tracing *C*.

A densogram of the pulmonary arch is easily recorded. The tracing is similar to that recorded with the slit upon the border of the vessel. It may be necessary to record this densogram whenever the contour of the pulmonary artery is obscured by hilar shadows or pulmonary consolidation.

Hilar Shadow (Figs. 9, *B* and 10, *B*).—The tracing of the hilar shadow is a densogram and represents the variations in the opacity of the hilar region caused by changes in the blood content. A comparative study has shown that the amplitude of the normal hilar pulsation is approximately between one-half and two-thirds that of the pulsation of the pulmonary arch. Additional pulsatory phenomena transmitted from the heart and great vessels influence the tracings of the hilar vessels. However, our studies have led us to the conclusion that these influences do not detract from the value of hilar vessel tracings.

When sufficiently amplified, the record of the hilar shadow appears as a typical arterial tracing. The pulsation of this structure occurs approximately 0.04 second later than the pulsations of the pulmonary artery; the rise of the hilar pulse starts approximately 0.12 second after the beginning of the first sound complex. The peak of the pulse wave is reached at the time of or slightly after the main vibration of the second sound. It may be followed by a small notch and then by a small dicrotic wave. In some of the subjects, the main pulse wave is preceded by a negative wave which is synchronous with the peak of the carotid pulse.

While there is no doubt that the positive wave of the hilar pulse signalizes the arrival of the arterial pulse wave in the branches of the pulmonary artery, one may ask whether the pulsations of the pulmonary veins also influence this tracing. Actually, apart from the smaller depth of both the negative systolic wave and the presystolic wave, some tracings of the right auricle are similar to those of the hilus and lung. However, since the auricular contraction should increase rather than decrease the size of the pulmonary veins, this interpretation is not an acceptable explanation of the presystolic wave. On the other hand, the early systolic depression may be due to the acceleration of the pulmonic venous flow which takes place in that phase.

Lungs (Figs. 9, *C* and 10, *C*).—The densogram of the lung is a tracing which resembles that of the hilus. However, the following differences are present: (a) There is a greater delay in the rise of the pulse wave; this taking place from 0.16 to 0.18 second after the beginning of the first sound-complex, and about 0.04 second after the rise of the pulsation of the hilar shadows. (b) There may be a greater delay of the peak, this occurring from 0.08 to 0.10 second after the main vibration of the second sound-complex. (c) The curve is more rounded and exhibits no trace of either the predicrotic notch or the dicrotic wave.

On the other hand, both the presystolic and the early systolic downward waves, already noted in the hilar tracing, may be present in lung tracings. As changes in the venous content of the lung are also recorded by our tracing, it is possible that these waves, or, at least, their early systolic phase, are influenced by the effect of auricular and ventricular contractions.

A comparative study has shown that the normal hilar pulsation is about one-half the height of the pulsation of the pulmonary artery, and that the pulsation of the lung is about one-half the height of the hilar pulsation (Fig. 9).

Superior Vena Cava (Fig. 11, *A*).—A good tracing of this structure is seldom recorded in normal individuals in either the sitting or the recumbent position.

Occasionally, it is possible to obtain a tracing which resembles the jugular tracing and which shows classically the three positive waves, on which are superimposed smaller vibrations apparently of transmitted origin. The first is an early systolic wave which is sharp and well defined; the second is midsystolic; and the third, extremely variable in position, is a wave which takes place in either early or mid-diastole.

Inferior Vena Cava (Fig. 11, *B*).—This tracing is recorded far more easily than that of the superior vena cava, as long as the subject is able to hold his breath in deep inspiration. The best tracing is recorded with the patient in slight rotation toward the right oblique.

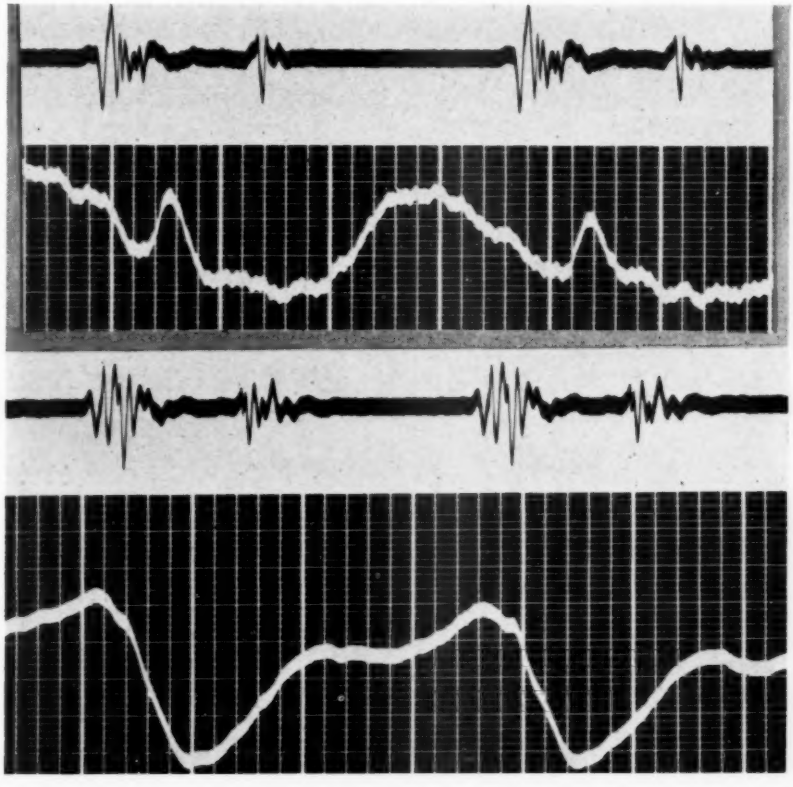

Fig. 11.—Tracings: *A*, of the superior vena cava in Position 11; *B* of the inferior vena cava in Position 7.

The inferior caval tracing presents two positive and two negative waves. There is a small presystolic positive wave, apparently due to the slower flow of blood at the time of the auricular contraction (the "*a*" wave). This is followed by a deep and sharp negative wave at the time of the arterial pulse (systolic collapse). Then follows a slow rise which culminates in a single, or double, peaked wave about 0.10 second after the second sound (the "*v*" wave). This

apparently is due to the slow engorgement of the vein occurring while the tricuspid valve is closed. The drop which follows occurs after the valve opens. The collapse reaches its maximum depth after the middle of diastole (diastolic collapse). No "*c*" wave is observed in the tracing of the inferior vena cava.

The tracing of the inferior vena cava is similar to that of the liver in a normal person and is the result of the same physiologic phenomena.

DISCUSSION

Fluorocardiograms show great similarity to tracings recorded on animals in open chest experiments, that is, plethysmograms, intracardiac pressure curves, intra-arterial and intravenous tracings, and suspension curves. In spite of

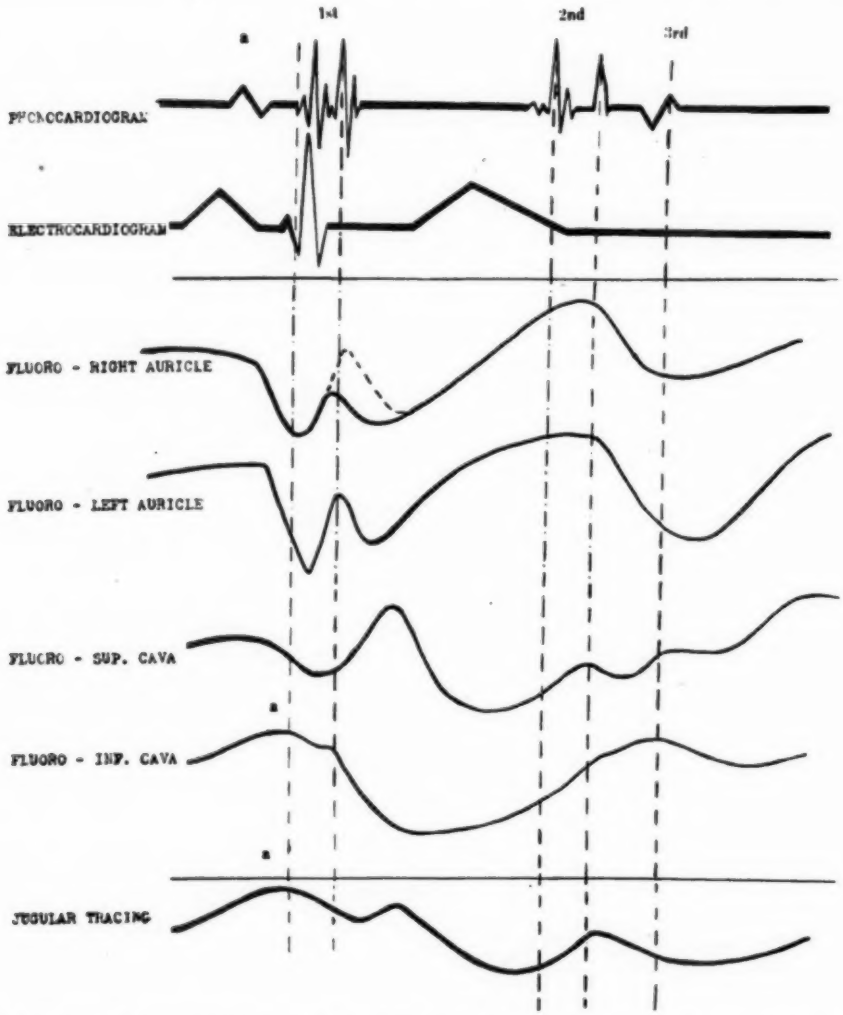

Fig. 12.—Schematic fluorocardiograms of the auricles and large veins and their time relation with various other clinical tracings.

certain limitations of fluorocardiography, due to anatomic and physiologic factors,[2] the close similarity of these tracings with the established physiologic facts proves the applicability and value of the method.

The timing of the different waves is easily obtained from a phonocardiogram simultaneously recorded. This clinical tracing gives more detail than an arterial tracing, is not modified by slow transmission of the waves (like a jugular tracing), and is more easily and more constantly recorded than a cardiogram.

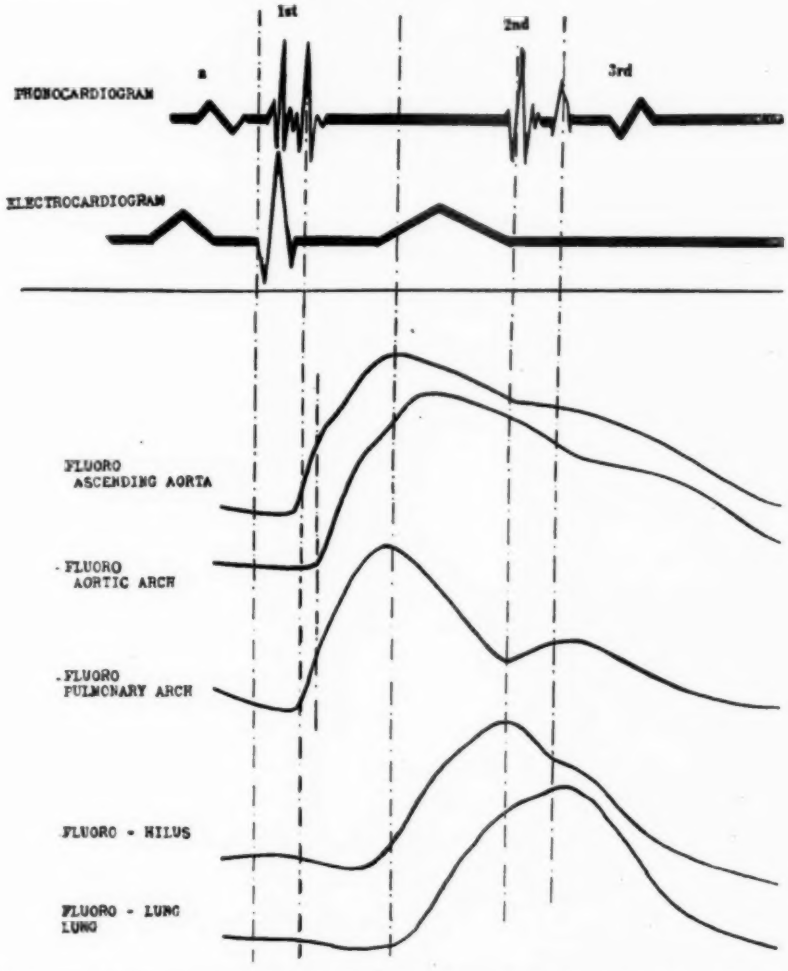

Fig. 13.—Schematic fluorocardiograms of the great vessels and lung, illustrating the time relationship with other clinical tracings.

The use of the electrocardiogram as a timing device is less exact because of the variable time relation between the action currents and the contraction phenomena. The electrocardiogram might have a limited value as a timer in patients with loud or continuous murmurs, but only for the purpose of deciding where ventricular systole begins.

Fluorocardiography permits the study, not only of the motion of cardiac chambers and of the large vessels, but also of certain other structures, such as the medium-sized (hilar shadows) and small (lung parenchyma) pulmonary vessels, and the inferior cava, which have not been accessible by other means.

In the study of the various cardiovascular structures, the following points are considered:

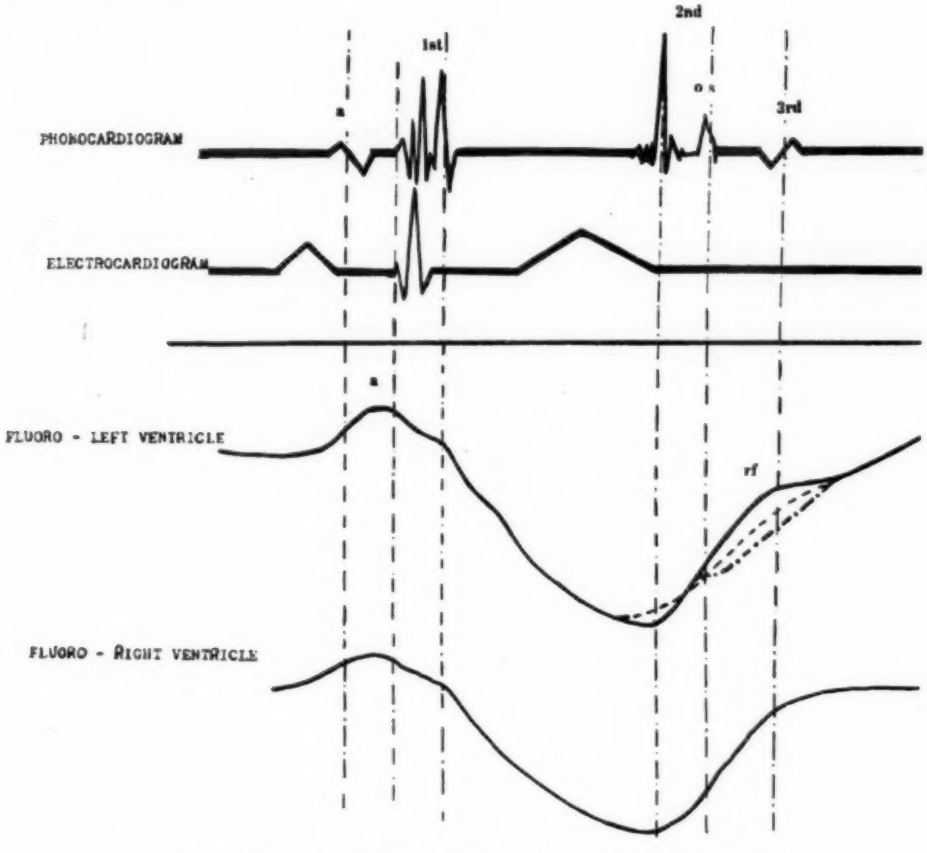

Fig. 14.—Schematic fluorocardiograms of the ventricles and their time relation with other clinical tracings.

(a) *The amplitude of pulsation*: This can be evaluated by comparing the amplitude of pulsations of one structure with that of another, where the pulsations of both structures are recorded with the same degree of amplification.*

(b) *The shape and time of various waves*: These can be evaluated by the use of optimum amplification and by timing the tracing with a phonocardiogram.

(c) *Abnormal movements*: Transmitted and inherent pulsation can be differentiated.

*The degree of amplification can be evaluated by a scale, marking the position of the dial. However, the degree of motion or density change of the cardiac silhouette cannot be expressed in exact numbers. Such a standardizer seems to be within the realm of possibility.

(d) *Dissociation between various chambers* (dissociation between the auricles, bundle branch block, A-V block): This is best accomplished by simultaneously recording the pulsations of the two chambers being studied, using two fluorocardiograms and a phonocardiogram.

Rappaport and Sprague[5] have shown that the first heart sound is composed of four components. Among these, the following are the most important for timing purposes: (1) a large vibration which occurs at the beginning of the isometric contraction of ventricular systole, and is due to the closure of the mitral and tricuspid valves; (2) another large vibration which occurs at the beginning of the ejection period of ventricular systole, and is caused by the opening of the semilunar valves.

In the second sound, as analyzed by Rappaport and Sprague,[5] the following vibrations have importance for timing purposes: (1) a group of high vibrations, which are caused by the closure of the semilunar valves at the end of ventricular systole; and (2) a small vibration which is caused by the opening of the mitral and tricuspid valves at the beginning of ventricular diastole.

The coincidence between vibrations of the phonocardiogram and waves of the fluorocardiogram confirms the interpretation of the various waves and vibrations of the sound tracing, as advocated by previous investigators;[4,5] in particular, it has been confirmed that:

(a) Two different vibrations of the first sound-complex often mark the closure of the A-V valves and the subsequent opening of the semilunar valves.

(b) The main vibration of the second sound-complex is due to closure of the semilunar valves, while the subsequent opening of the A-V valves takes place later and is frequently marked by another small vibration.

(c) The third sound is due to the rapid filling of the ventricles in early diastole.

Figs. 12, 13, and 14 have been constructed on the basis of our tracings in order to facilitate comparison.

SUMMARY AND CONCLUSIONS

Fluorocardiograms (electrokymograms), recorded over various cardiovascular structures, have been studied in twenty normal subjects. These tracings are compared with simultaneously recorded phonocardiograms.

The identification of the various waves and their relation to the phases of the cardiovascular dynamics are discussed. They may be attributed to two different phenomena: (1) motions of the x-ray silhouette caused by changes in volume in systole and diastole, and (2) motions due to rotation, traction, or total shift due to contraction or dilatation of either the same or some other cardiovascular structure.

The tracing of the apex reveals a small positive wave due to completion of filling as the effect of auricular contraction, a small subsequent notch and a deep negative wave in systole, a rapid rise in early diastole, and a slow rise later.

The causes of these phenomena are discussed. The possible lack of coincidence between the deepest point of the systolic wave and the second sound is attributed to displacement of the ventricular mass. Tracings recorded over any other point of the left ventricle give smaller waves and a faithful expression of ventricular systole. The same is true for the right ventricle, whose contraction can be recorded in the lateral positions.

Both left and right auricular tracings reveal first the results of auricular contraction, then a decrease of auricular volume due to ventricular traction over the A-V septum, and later a collapse in early diastole. The causes of the three negative waves are analyzed.

A tracing of the ascending aorta is possible in the left oblique position and occasionally, in the posteroanterior position. It is recorded in the latter position in older people because of atherosclerosis and dilatation of the aorta.

The tracing of the aortic knob has all the characteristics of a "central" pulse; that of the pulmonary knob presents a smaller anacrotic depression and a higher dicrotic wave, often resembling the tracing of a peripheral pulse.

The tracings of the hilar shadows and of the lung parenchyma are analyzed and discussed. They reveal a slowly moving arterial pulse in the pulmonary circulation.

A good tracing of the superior vena cava is seldom recorded in normal subjects, either young or old. It is more commonly recorded if there is venous engorgement. On the other hand, the tracing of the inferior cava is obtained frequently. It shows a positive wave in presystole, a deep systolic collapse, and a diastolic collapse. It resembles the liver tracing of a normal subject.

A widely accepted interpretation of the phonocardiogram is confirmed by fluorocardiography.

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Errata

In the January, 1948, issue of the JOURNAL, Fig. 1, p. 135, and Fig. 2, p. 137, were inserted upside down in the article entitled "Paroxysmal Auricular Tachycardia at a Rate of 86 Per Minute," by Ralph Miller, David Biber, and Julius S. Perelman.

In the article entitled "Reactions to Decholin as Used in Circulation Time Determination" by James J. Norman, which appeared in the November, 1947, issue of the JOURNAL, the described reactions were incorrectly attributed to "Decholin." Actually, the material used was Sodium Dehydrocholate Solution, manufactured by Lederle Laboratories, Inc., New York, N. Y., and not the product manufactured by the Ames Company of Elkhart, Ind., (which now owns the trademark "Decholin") or Riedel-de Haen, Inc., New York, N. Y.

American Heart Association, Inc.

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THE FEBRUARY ISSUE

The Editorial Board and the C. V. Mosby Company are delighted to be able to devote this entire issue to the scientific papers presented at the last Annual Meeting.

The preparation and publication of a large special issue is not yet a simple matter. In spite of the difficulties, all papers, except those which have been published already or are to be published elsewhere, are being included in the approximate order of their presentation.

The special preparation which some of the papers have required prevents their presentation in this issue. These postponed papers, which will appear in subsequent issues, include The George Brown Memorial Lecture, given by Dr. Helen Taussig and Dr. Alfred Blalock, and the presentations of Dr. Joseph T. Roberts, Dr. Myron Prinzmetal and associates, Dr. John Schweppe and associates, and Doctors Harold K. Moss and Louis G. Herrmann.

The necessity of omitting the Discussions is regretted.

MEETING OF THE INTER-AMERICAN SOCIETY OF CARDIOLOGY

The Inter-American Society of Cardiology has authorized the meeting of the III Inter-American Cardiological Congress, to be held in Chicago, Ill., at the Michael Reese Hospital, from June 13 to June 17, 1948. This meeting will take place immediately before the American Heart Association annual meeting, June 18 and 19, and the American Medical Association meeting, the week of June 20. Inquiries regarding the Congress may be addressed to the offices of the III Inter-American Cardiological Congress, at the Michael Reese Hospital, Chicago, Ill.

ANNUAL MEETING

The Annual Meeting and Twenty-first Scientific Session of the American Heart Association will be held in Chicago, Illinois, on June 18 and 19, 1948. The Stevens Hotel will be the headquarters for all meetings and for the Annual Dinner which will take place on Saturday evening, June 19.